FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE

(ODAC)

Wednesday, January 7, 2015

8:00 a.m. to 3:54 p.m.

FDA White Oak Campus

Building 31, The Great Room (Room 1503)

White Oak Conference Center

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. ARMSTRONG: Good morning, and welcome to this meeting of the Oncology Drugs Advisory Committee. I'd first like to remind everybody to please silence your cell phones, smartphones, and any other electronic devices, if you haven't already done so. I'd also like to identify the FDA press contact, Sandy Walsh. If you're present, please stand.

Now I'd like to go around the table and have the panel members introduce themselves. We'll start with Dr. Fingert.

DR. FINGERT: Good morning. I'm Howard Fingert. I'm a hematologist-oncologist and I'm the industry representative, nonvoting, and I'm employed at Takeda Pharmaceuticals.

DR. MOREIRA: Good morning. I'm Antonio Moreira. I'm a bioprocess engineer. I am with the University of Maryland, Baltimore County, where I'm vice-provost for academic affairs and professor of chemical, biochemical, in environmental engineering.

DR. STRONCEK: I'm Dave Stroncek. I'm a hematologist and oncologist from the NIH Clinical Center.

DR. MAGER: Good morning. Donald Mager at the University of Buffalo. I'm associate professor of pharmaceutical sciences.

DR. WALDMAN: I'm Scott Waldman. I'm from Thomas Jefferson University in Philadelphia. I'm an internist and cancer clinical pharmacologist, and I'm the chair of Pharmacology and Experimental Therapeutics.

DR. NEVILLE: Good morning. I'm Kathleen Neville. I'm at Children's Mercy Hospital in Kansas City. I'm a pediatric hematologist-oncologist and clinical pharmacologist, and I direct the early phase program there.

DR. BENSINGER: I'm William Bensinger. I'm a hematologist-oncologist, at the University of

Washington in Seattle.

DR. LAPORT: I'm Gina Laport, a medical oncologist and bone marrow transplant physician for adult patients at Stanford University.

DR. FOJO: I'm Tito Fojo, medical oncologist, National Cancer Institute.

DR. ROTH: Bruce Roth, medical oncologist, Washington University in St. Louis.

DR. ARMSTRONG: I'm Deb Armstrong, medical oncologist, Johns Hopkins in Baltimore and chair of the ODAC.

DR. BRIGGS: Caleb Briggs, designated federal officer, ODAC.

DR. COLE: Bernard Cole, biostatistics, University of Vermont.

DR. LIEBMANN: James Liebmann, University of Massachusetts, medical oncologist.

DR. ZONES: Jane Zones. I'm the consumer representative. I'm a medical sociologist and affiliated with Breast Cancer Action and the National Women's Health Network.

DR. HILLARD: Hi. Randy Hillard. I'm a

psychiatrist at Michigan State University, but I'm here as your patient representative today. Stage 4 metastatic stomach cancer 2010. I wake up every morning shocked at how non-dead I am.

(Laughter.)

DR. PAZDUR: Richard Pazdur, office director.

DR. KAMINSKAS: I'm Edvardas Kaminskas. I'm deputy director, Division of Hematology Products. I'm sitting here for Ann Farrell, who's the director of hematology products division. And she's out sick today, so I'm substituting for her.

DR. CHRISTL: Leah Christl, associate director for therapeutic biologics in the Office of New Drugs.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the director of the Office of New Drugs at FDA.

DR. KOZLOWSKI: Steven Kozlowski, director of the Office of Biotechnology Products at the FDA.

DR. ARMSTRONG: Thank you all.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson, and we look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during breaks or lunch. Thank you.

I'll pass it on to Caleb Briggs, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. BRIGGS: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of the committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and, for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves the Biologics License Application 125553 for EP2006, a proposed biosimilar to Amgen, Incorporated's Neupogen, filgrastim, submitted by Sandoz, Incorporated. The proposed indications for this product are:

1) to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever;

2) for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with acute myeloid leukemia;

3) to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation;

4) for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and

5) for chronic administration to reduce the incidence and duration of sequelae of neutropenia, e.g., fever, infections, oropharyngeal ulcers, in symptomatic patients with congenital neutropenia,

cyclic neutropenia, or idiopathic neutropenia

This is a particular matters meeting during which specific matters related to Sandoz's EP2006 will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the products at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Howard Fingert is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Fingert's role at this meeting is to represent industry in general and not any particular company. Dr. Fingert is currently employed by Takeda Pharmaceuticals.

We would like to remind members and

temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ARMSTRONG: Thank you.

We will proceed now with opening remarks from Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research at FDA.

Opening Remarks – Janet Woodcock

DR. WOODCOCK: Thanks very much, and good morning everyone. I'd like to welcome the members of our advisory committee. I'm really glad that we had this today and not yesterday. We have a quorum here, and we'll be able to hold this meeting. The attendees of this meeting as well, welcome to what

I think is a historic occasion.

This is the first application under our new biosimilar pathway that's being brought to an FDA advisory committee. This is a culmination of many years of work for me and many other people. And so, I'd like to thank the many FDA staff who've really worked very hard over many years to shape the standards and policies, and this includes today's presenters, but also many other people who've worked on this project.

Now, many countries worldwide are initiating biosimilars' programs now, and I am frequently asked why the EU, European Union, is ahead of the U.S. in biosimilars. They have a number of products on the market now. And the simple answer is that the statutory pathway was established much earlier in Europe. And so they have been working on that for some time and had a statutory pathway available.

Once the U.S. Congress created legislation, and it was a signed into law, the U.S. then had a pathway that the FDA could use, and that is what this application is under today. And since this time that the law was passed, the sponsor community, the pharmaceutical development community, has been extremely busy in working on developing products that would be biosimilars in the United States, and our program has been very busy.

Of course, much of this work has been not public because they’re doing their development programs, their manufacturing programs, and their comparative programs. But today we're actually going to hear about one of these programs, and I think is a very historic occasion.

We have had a great deal of activity in the biosimilar development program, and so, we expect this will be the first of a number of meetings that we have assessing applications.

Now, developing and implementing a new drug approval pathway in the United States can be challenging I think for FDA, for sponsors, for the medical community and for the public for a variety of reasons. We had many challenges years ago with our generics program, developing the standards and also dealing with concern and skepticism are generics the same. And these, of course, are small molecule generic drugs, although some of them may be quite complex.

Today, about 85 percent of dispensed prescriptions in the United States are generics, and so this program is really -- the generics in the United States are providing medical care for much of our population. Some skepticism remains about small molecule generics in certain distinct areas, and we're doing additional research to address these questions, but the benefits to the public have been shown for generics and they have been tremendous.

We have a new user fee program that we're operating in the generic world because of the huge success of the industry and the massive volume of generic applications that we are now receiving every year. So we are now just at the beginning of our new biosimilar program. And of course, biosimilars are not -- the biosimilar program is about proteins. It is not about small molecules, and they're very different. And there's many more challenges in the comparisons in determining comparisons with a reference drug.

As we started the program, what we encountered both internally at FDA and what I've heard from the developers who are working on this on the outside, and also we've heard from our colleagues in the medical community, what I call cognitive dissonance. And what is that?

Well, we are used to seeing adequate and well-controlled trials in development programs for new drugs and large outcome trials often, and that's often what's brought before the ODAC and other advisory committees. And that's to demonstrate safety and efficacy of a new drug, and that is our standard, that we would have substantial evidence.

Here, what we are doing is, under the statute, we are looking for demonstration of biosimilarity. And what everyone said, well, where are the two adequate and well-controlled trials for all these biosimilar development programs that we would expect? We're not showing safety and efficacy; that's been shown for the reference-listed drug. We are looking for a finding of biosimilarity.

That's what I mean by cognitive dissonance, is taking everyone, both internally I think in the companies, and now it's going to be with public discussion to get their heads around, what does a demonstration of biosimilarity look like? And we have published guidance, and we have published a lot of information and given talks and so forth, and what you'll hear today is our thoughts about that.

We think this is completely possible. We think it is rigorous, it can be done rigorously, but it is different, and it is the start of a new program. We're going to have to understand that we're talking about a different kind of development program than the kind of development program that you would do for a new drug or a new indication for a new drug.

Now some cases of development and showing of biosimilarity may be less complex than others, and this is true in the world of generics as well. In the case of biosimilars, we have sometimes molecules that are simpler, and we have some molecules that are much more complex. And so that's a factor that has to be taken into account as we make these comparisons to the reference drug.

Also, some drugs have good pharmacodynamic endpoints that are well understood by the community and that are a good guide to many of their properties in humans, and some drugs may not have those pharmacodynamic endpoints. And what we have seen are large empirical trials to show their benefit in humans. Therefore, we don't have as much of guidepost for comparison.

Regardless of all this, I believe a biosimilar program that we will develop over time will provide benefits to the public and will provide biosimilar drugs that provide the same clinical performance for patients and for the clinicians, and yet provide that access in the

United States that's so important for our patients.

So today is another step along this pathway. It's been a long pathway, and I hope that you'll keep these thoughts in mind with your deliberations. And Dr. Christl will be going in much more detail into the statute and how it is structured to evaluate biosimilarity and interchangeability. Thank you.

DR. ARMSTRONG: Thank you, Dr. Woodcock.

Next, Dr. Leah Christl will continue the FDA presentation. She's the associate director for therapeutic biologics, the Office of New Drugs.

FDA Presentation - Leah Christl

DR. CHRISTL: Good morning, everyone. We're having a little technical difficulty here, but hopefully this will get fixed in a moment. As was said, my name is Leah Christl. I am the associate director for therapeutic biologics in the Office of New Drugs in the Center for Drug Evaluation and Research at FDA.

I'm going to talk to you a little bit more about the regulatory pathway, give you a general overview of the regulatory pathway, and also give you an overview of FDA's guidance for the development and approval of biosimilar products in the U.S.

I want to note that this is a general presentation. This is not product specific. This is really an overview, again, of the statute and FDA guidance. We'll talk about some development concepts. This is not product specific. The presentations from the sponsor, as well as the subsequent FDA presenters, they will talk specifically about the development program that is the topic of discussion today. And you'll hear more from those presenters about how it is that this particular development program fits into the general development concepts that I'm going to be discussing.

So today, I'm going to go over some background about the statute, give you some definitions, and talk about the approval pathway in terms of the general requirements. Again, walk you through the general concepts in the statute, give you some familiarity with the terminology to help set the stage for the subsequent presentations.

I'll then move on to some specific development concepts about biosimilars. Discuss briefly what guidances FDA has published to date, and then talk more generally about the approach to development, and then touch on some specific development concepts.

So the Biologics Price Competition and Innovation Act of 2009, or the BPCI Act, was passed as part of health reform under the Affordable Care Act, and it was signed into law March 23rd of 2010. What this did was that it created an abbreviated licensure pathway for biological products that are shown to be biosimilar to or interchangeable with an FDA licensed reference product. And we'll talk more about each of those terms.

So what do we mean by an abbreviated licensure pathway for biological products? What the statute says is that a biological product that is demonstrated to be highly similar to an FDA licensed biological product, or the reference product, may rely for licensure on, among other things, publicly available information regarding FDA's previous determination that the reference product is safe, pure, and potent.

So this licensure pathway permits a biosimilar biological product to be licensed under 351(k) of the Public Health Service Act, or PHS Act, based on less than a full complement of product-specific preclinical and clinical data. And that's what's meant by an abbreviated licensure pathway.

So the agency can license a biosimilar product based on less than a full complement of product-specific preclinical and clinical data. And we'll talk more in the subsequent slides about how that concept comes about in terms of the abbreviated licensure pathway and where the data comes from and the comparisons to the reference product.

So to give you some familiarity with the terms that you're going to be hearing today, biosimilar or biosimilarity is defined in the Act to mean that the biological product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product.

So both of these standards here, the highly similar and no clinically meaningful differences, are a part of the demonstration of biosimilarity and both need to be demonstrated in order for a product to be licensed as a biosimilar.

What do we mean by reference product? The reference product is defined as the single biological product that's licensed under Section 351(a) of the Public Health Service Act against which a biological product is evaluated in an application submitted under Section 351(k) of the Public Health Service Act.

When we talk about the subsections of the Public Health Service Act, 351(k) is what you can think of as covering the biosimilar and interchangeable products. 351(a) is what covers the reference products. For lack of a better term, the standalone development programs is a good way to think about it.

So biological products that are licensed by FDA under 351(a) of the Public Health Service Act are approved based on a full complement of clinical and preclinical data to support approval. Again, under 351(k), the biosimilar interchangeable products, those are licensed based on less than a full complement of preclinical and clinical data, product-specific preclinical and clinical data, based on comparisons to this reference product that, again, was approved based on a full complement of product-specific preclinical and clinical data.

So the definition of interchangeable or interchangeability is also in the Act, and it means the biological product is biosimilar to the reference product. So in other words, it meets those standards of being highly similar, no clinically meaningful differences. And it can be expected to produce the same clinical result as the reference product in any given patient. For a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the product and its reference product, is not greater than the risk of using the reference product without such alternation or switch.

It's also noted in the statute that an interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.

We wanted to give you a good overview of the statute today and give you the definition of interchangeability, but I do want to note that the application from Sandoz to be discussed today requests approval as a biosimilar, not as an interchangeable product. So the standard, again, is highly similar with no clinically meaningful differences for a biosimilar product.

So the Act outlines what a 351(k) application -- so an application for a biosimilar product must include. The application must include information demonstrating that the product is biosimilar to the reference product; that it utilizes the same mechanism or mechanisms of action for the proposed condition or conditions of use, but only to the extent that the mechanism or mechanisms are known for the reference product.

The condition or conditions of use proposed in labeling for the product have been previously approved for the reference product. The proposed product has the same route of administration, dosage form and strength as the reference product. And it is manufactured, processed, packed, or held in a facility that meets the standards designed to assure that the biological product continues to be safe, pure, and potent.

So these are additional requirements for the products. So again, the standard for biosimilarity is highly similar with no clinically meaningful differences. This is additional information and additional demonstration regarding the same mechanism of action, conditions of use, same route of administration, et cetera.

So the type of data that we would expect to be submitted in a 351(k) application is also outlined in the Act. So it requires that the application include, among other things, information demonstrating biosimilarity based on data derived from analytical studies that demonstrate that the product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components; can include animal studies, including an assessment of toxicity; and a clinical study or studies, including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics, that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed, and for which licensure is sought for the biosimilar product.

The statute does state that FDA may

determine in its discretion that an element that's described above is unnecessary in a biosimilar application in order to demonstrate biosimilarity or interchangeability.

So the FDA shall license a biological product under 351(k) of the PHS Act if the agency determines that the information in the application or supplement is sufficient to show that the biological product is biosimilar to the reference product, so it meets the standards that are outlined in the Act, or it meets the standards that are described for interchangeability with the reference product and an applicant or other appropriate person consents to inspection of the facility.

So of note, the BPCI Act does not require that FDA promulgate guidance or regulation before reviewing or approving a 351(k) application. Again, FDA has issued a number of draft guidances regarding the development of biosimilar products, and I will mention those briefly.

While the BPCI Act defines reference

products -- again, it's what the biosimilar needs to demonstrate they're biosimilar to or interchangeable with -- and reference product is defined in the Act as the single biological product that's licensed by FDA under 351(a) of the Public Health Service Act, the FDA has articulated in draft guidance that data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-U.S.-licensed product may be used to support a demonstration of biosimilarity to a U.S.-licensed reference product.

If this approach is taken in a development program, the sponsor should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity, and establish an acceptable scientific bridge to the U.S.-licensed reference product.

If a sponsor takes this approach, again, they need to support their approach. And the type of bridging data that would need to be included includes direct physical chemical comparison of all three products: the proposed biosimilar compared to the U.S.-licensed reference product; the proposed biosimilar compared to the non-U.S.-licensed comparator product; and the U.S.-licensed reference product compared to the non-U.S.-licensed comparator product.

The bridge likely will include a three-way bridging clinical PK and/or a PD study, and all three pairwise comparisons that I described should meet the prespecified acceptance criteria for analytical and PK and/or PD similarity.

I will note that a sponsor should justify the extent of the comparative data needed to establish a bridge to the U.S.-licensed reference product, and there are a number of factors that can come into play in terms of justifying the extent of the scientific bridge that is necessary.

Moving into an overview of the approach to the development of biosimilars, again, we'll discuss some of the scientific concepts. As I noted, FDA has published a number of draft guidances that are related to specific development concepts around the development of biosimilar products. They’re listed here along with their publication dates. We won't go into detail about those, but I will be describing the development concepts that are described in each of these guidances.

The FDA draft guidance that has been issued to date focuses on therapeutic protein products. They’re general guidances. They are not product-specific guidances, and they discuss general scientific principles around the development and approval of biosimilar products.

These guidances outline a stepwise approach to generating data to support a demonstration of biosimilarity and the evaluation of residual uncertainty at each step. The guidances also introduce the concept of the totality of the evidence approach to support the approval of biosimilar products and we'll talk about the stepwise evidence development along with the totality of the evidence in the upcoming slides.

Moving into the key development concepts, again, I want to remind folks that these are the general development concepts. This is not product specific. So this is what FDA has articulated in their draft guidance in a general manner.

As was noted by Dr. Woodcock, the goals of the standalone development program in a biosimilar development program are different. So the goal of a standalone development program is to demonstrate that the proposed product is safe and efficacious. Drug development follows a very well-understood pathway, a well-accepted pathway, starting with preclinical research, moving on to phase 1 and phase 2 studies, and then culminating in phase 3 or pivotal trials to demonstrate safety and efficacy in each of the conditions of use for which licensure is requested.

The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed product and the reference products. The goal is not to independently establish safety and effectiveness of the proposed product. As Dr. Woodcock noted, the reference product already did this.

Again, that product was approved based on a full complement of product-specific preclinical and clinical data, would have adequate and well-controlled clinical trials for each condition of use for which licensure was requested. So the reference product already established safety and effectiveness. So the goal for the biosimilar development program is to demonstrate biosimilarity between the proposed product and the reference product.

What does this mean from a development standpoint? As I mentioned, FDA has outlined this concept of stepwise evidence development for biosimilar development programs, and the stepwise approach is for the generation of data and support of a demonstration of biosimilarity.

This includes the evaluation of residual uncertainty about the demonstration of biosimilarity at each step. FDA has also articulated a totality of the evidence approach in evaluating biosimilarity. And this really comes out or means that there's no one "pivotal study" that demonstrates biosimilarity. It's a culmination of all the data that's developed and generated through the stepwise approach, and it's the totality of the evidence that supports the demonstration of biosimilarity.

Sponsors apply a stepwise approach to data generation and to the evaluation of residual uncertainty at each step. The questions that would be asked during this for a development program while a sponsor generates data is what is the residual uncertainty about biosimilarity, of meeting those standards of highly similar with no clinically meaningful differences?

What differences between the reference product and the proposed product have been observed based on the studies that have been conducted at any point during the development program and how best should those differences be evaluated in terms of their potential impact on the clinical performance of the product?

What studies should be conducted to address the residual uncertainty? What's the best way to evaluate the impact of the residual uncertainty?

Again, with this totality of the evidence concept, there's no one study that's pivotal to demonstrate biosimilarity, there's no one size fits all assessment either in this concept. So again, as Dr. Woodcock had mentioned, there's a variety of complexity of biological products. Some are, for lack of a better term, more simple biological products; other ones are more complex.

The concept of residual uncertainty in what differences could be observed in a particular development program may differ from program to program and product to product. So there's no one size fits all assessment for this. In that totality of the evidence, the sponsor and the agency need to look at all of the data that's generated to support that demonstration of biosimilarity. And the FDA scientists will evaluate the applicant's integration of various types of information to provide the overall assessment that the biological product is biosimilar to a U.S.-licensed reference product.

The stepwise approach begins with analytical similarity assessment, and the analytical similarity data is really the foundation of a biosimilar program. This is that starting point of building that totality of the evidence.

When we talk about the analytical similarity data, this is where a sponsor will conduct extensive structural and functional characterization of the reference product and the proposed product. They need to understand the molecule and the function, identify the critical quality attributes and the clinically active components. And this is all done to understand the relationship between the quality attributes and the clinical safety and efficacy profile, and this aids in the ability to determine residual uncertainty about biosimilarity and to predict expected clinical similarity from the quality data.

In generating the analytical similarity data, the sponsor needs to characterize the reference product quality characteristics and the product variability, and they need to characterize the proposed biosimilar product quality characteristics and the product variability.

What they need to do is they need to develop a manufacturing process for the proposed biosimilar product that's designed to product a product with minimal or no differences in product quality characteristics compared to the reference product. Again, this is that foundation of developing a biosimilar product.

The proposed biosimilar product, again, must be demonstrated using analytical studies to be highly similar to the reference product. If you'll remember when we went through the general concepts that are outlined in the Act, it talked about the types of data, which can include analytical data that demonstrates the product is highly similar, notwithstanding minor differences in clinically inactive components.

As part of the analytical similarity assessment, FDA recommends that a statistical analysis of the analytical similarity data be conducted. The statistical analysis is conducted to support a demonstration that the proposed biosimilar product is highly similar to the reference product. This is a piece or a part of the analytical similarity assessment.

The sponsor should consider criticality of risk rankings of the quality attributes with regard to their potential impact on activity, PK and PD, safety, and immunogenicity. And FDA recommends that sponsors use a tiered approach for assessment, so first looking at that criticality ranking of the quality attributes based on their potential impact, if there are differences.

Then there could be equivalence testing for some of the high risk attributes, quality ranges, plus/minus a certain standard deviation for other high to low risk attributes, or raw/graphical comparisons for other attributes. And this really has to be discussed within the context of a specific development program. And this is, again, going to depend on that criticality ranking.

Just because something is a high risk in terms of the criticality ranking, depending on the type of attribute, the assay to assess for that attribute, it may or may not fit into one of these statistical testing approaches in terms of equivalence testing of quality ranges or raw, graphical comparisons.

Not everything that is a high-risk attribute will get equivalence testing. You have to think about what's right for the data that you're working with, which is why FDA recommends not only doing this criticality ranking, but then also putting them into the statistical testing tiers. Again, this has to be a conversation between the agency and the sponsor within the context of a specific development program.

I will note that FDA is continuing to consider these issues and intends to develop guidance for industry as appropriate on this topic.

In moving out of the analytical similarity assessment, what you do with it at this point, what the sponsor needs to do at this point, is to look at the analytical similarity data, look at the comparisons between the reference product and the proposed biosimilar product and identify any differences in the quality attributes, and then evaluate the potential impact of differences that are observed in the analytical similarity assessment.

The potential effect of the differences on safety, purity, and potency should be addressed and supported by appropriate data. And these observed differences and the evaluation of their potential impact is what drives the rest of the development program of what additional data is necessary to demonstrate biosimilarity.

In considering animal data as a part of the biosimilar development program, animal toxicity data are useful when there are uncertainties that remain about the safety of a proposed product prior to initiating clinical studies. And the scope and extent of animal toxicity studies will depend on the publicly available information and/or data submitted in the biosimilar application regarding the reference product and the proposed biosimilar product, and the extent of known similarities or differences between those two products.

In some programs, a comparison of PK and PD in a relevant animal model may also be useful. But again, this needs to be discussed within the context of a specific development program, and there are product specific considerations that will come into play.

The next area is clinical studies, in terms of the demonstration of biosimilarity, so moving through the stepwise evidence development, looking at the analytical similarity data, animal data, if it's considered necessary or relevant, and then moving into the clinical studies.

So the nature and the scope of the clinical studies will depend on the extent of residual uncertainty about biosimilarity of the two products after conducting the structural and functional characterization, and where relevant, the animal studies. So again, this all builds on each other. All the data builds on each other moving through the stepwise evidence development.

The type of clinical data that would be expected in a biosimilar development program is a scientific matter. FDA expects an adequate clinical PK and PD of relevant comparison between the proposed biosimilar product and the reference product. Also, as a scientific matter, at least one clinical study that includes a comparison of the immunogenicity of the proposed and reference product will generally be expected.

Also, as a scientific matter, a comparative clinical study would be necessary to support a demonstration of biosimilarity if there are residual uncertainties about whether there are clinically meaningful differences between the proposed and reference product based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment. So again, you can see how this evaluation all builds on itself.

Speaking more specifically about the clinical data and the types of studies that would be conducted, and first talking about the comparative human PK and PD data, FDA has articulated in draft guidance that the human PK and PD data in a biosimilar program are intended to demonstrate PK and PD similarity. So again, it's a comparative assessment between the proposed product and the reference product, demonstrating PK or PD similarity between the products. And this goes toward assessing clinically meaningful differences between the proposed biosimilar and the reference product.

PK and/or PD is generally considered the most sensitive clinical study or assay in which to assess for differences should they exist between the products. And this is why it's that first piece of clinical data that is a scientific matter FDA would expect to be included in a biosimilar development program.

The concept of this in terms of looking at why it's a sensitive assay to support a demonstration of biosimilarity is that this is with the assumption that similar exposure and pharmacodynamic response, if it's possible, provide similar efficacy and safety. In other words, there's an exposure/response relationship that exists. So again, clinical PK data will generally be expected, and PD data are desirable, but it's a case-by-case determination.

There are a number of factors to consider when thinking about PK and PD study design in the context of a biosimilar development program. We'll go through some of them here. They include study population.

In that PK or PD study, it should be conducted in an adequately sensitive population to detect differences should they exist. And in terms of PD endpoints, it should reflect the biological effect or effects of the drug. However, they may or may not be on the mechanistic path of the mechanism of action or disease progression.

It should also be considered what the best route of administration is to test for if the reference product is licensed and the biosimilar applicant is seeking licensure for more than one route administration, about what's the more sensitive population to test in and to detect differences should they exist, and also to give you other information possibly about the safety of the product.

If there are multiple routes of administration versus a single route of administration, there has to be consideration of what route of administration needs to be considered.

So the data analysis plan for these PK and PD studies, FDA has articulated in draft guidance that the acceptance range of 80 to 125 with a 90 percent confidence interval for PK and PD is a good starting point. It's a good baseline. However, a sponsor can scientifically justify the use of other ranges. And again, there are product specific considerations that might relate to intra or inter product or patient variability in PK that would need to be considered. The choice of primary endpoints that FDA recommends include for PK, AUC and Cmax, and for PD, AUEC.

There are other considerations in the PK and

PD studies. This includes an evaluation of the incidence of immunogenicity. FDA recommends that in any clinical study that's conducted for a proposed biosimilar that immunogenicity is evaluated.

So moving into the comparative clinical study considerations, just to give folks a little bit of clarity around this, when we talk about a comparative clinical study, in terms of a biosimilar development program -- we've spoken about the comparative PK and PD assessment. When we talk about a comparative clinical study, it's more of a traditional safety and efficacy study. But again, the intent of that study is not to independently establish the safety and effectiveness of the biosimilar, so we refer to it as a comparative clinical study in the context of a biosimilar development program.

A comparative clinical study for a biosimilar development program, if it's considered necessary, if there are residual uncertainties about whether there are clinically meaningful differences, again should be designed to investigate whether there are clinically meaningful differences in safety and effectiveness between the proposed product and the reference product.

In thinking about the appropriate study design for a comparative clinical study in a proposed biosimilar development program, a sponsor and the agency would need to consider the adequacy of the population; the sample size and duration to detect differences should they exist. So again, it's a lot of the same considerations that would be thought about for a comparative PK and PD study for a biosimilar program. And again, the goal of the study is to support a demonstration of no clinically meaningful differences.

FDA has articulated in draft guidance that, typically, an equivalence design with symmetric, non-inferiority and non-superiority margins would be used, but other designs may be justified depending on the product-specific considerations, as well as program-specific considerations; again, looking at that totality of the evidence and what residual uncertainty exists about whether there are clinically meaningful differences between the products.

Again, to emphasize, FDA has articulated a totality of the evidence approach in demonstrating biosimilarity, and it includes the stepwise evidence development, beginning with the analytical similarity assessment as the foundation of the biosimilar program, and then moving up in this pyramid of each piece of data building on the other, looking at nonclinical studies, animal studies, clinical pharmacology studies, and then whether any additional clinical studies are necessary. So the highly similar analytical and the PK and PD similarity data assumes a lower risk of clinical differences.

FDA has also articulated in draft guidance that the potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed, based on extrapolation of clinical data intended to demonstrate biosimilarity in one condition of use.

If a sponsor takes this approach in their development program, sufficient scientific justification for extrapolating the data is necessary. Of note, other parties and stakeholders may interpret the term "extrapolation" in a different manner, but what is described in the first bullet is what FDA means when they discuss extrapolation.

So again, it's extrapolation of clinical data intended to demonstrate biosimilarity in one condition of use, to other conditions of use for which the reference product is licensed and the biosimilar is seeking licensure.

In terms of extrapolation considerations, again, the sponsor providing that adequate scientific justification, FDA draft guidance outlines the factors or issues that should be considered when providing scientific justification. And some of these are listed here as examples. It's not an exhaustive list. It's just a subset of what FDA has articulated in draft guidance.

These factors are issues to be considered include the mechanism of action in each condition of use for which licensure is sought, the PK and biodistribution of the product in different patient populations, the immunogenicity of the product in different patient populations, and differences in expected toxicities in each condition of use in patient population.

FDA has articulated, in guidance, the differences between conditions of use do not necessarily preclude extrapolation. Again, these factors or issues that should be considered are considered in the context of providing an adequate scientific justification to support extrapolation.

So these are the factors that need to be addressed, but it doesn't mean that just because there's differences a sponsor couldn't extrapolate. They just need to address those differences and provide appropriate data and information to support extrapolation in a specific program.

In summary, the content of a biosimilar development program is based on a stepwise evidence development and the evaluation of residual uncertainty about biosimilarity between the proposed biosimilar product and the reference product. An approval of the proposed biosimilar product is based on the totality of the evidence submitted by the biosimilar sponsor intended to demonstrate biosimilarity.

I thank you for your attention, and I think that we have time for clarifying questions from the committee if there are any.

Clarifying Questions to the Presenter

DR. ARMSTRONG: Thank you very much. Dr. Roth?

DR. ROTH: This may not be a good time for this question, but if not, tell me and can do this later. But I'm trying to wrap my arms around what it means to have a designation as a biosimilar, but not the designation of interchangeable at the end-user level. And so, let's say as a simplest example, you're a pharmacist that gets a prescription that has nothing -- as generic as it gets. It's written for G-CSF. And of course, a physician has not checked the box on the prescription.

Does that prescription get filled only with the reference product or does the pharmacist have options? Or by corollary, could a payer or pharmacy benefit manager, under that specific context, one not the other, designate a reference product as a certain tier and the biosimilar as a different tier product, making that decision for their members?

DR. CHRISTL: Caleb, I can't go back any further. I don't know if you can go back to the slide about interchangeability. Yes, that one.

So as is stated in the Act in terms of the definition of interchangeability, an interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product. And that's as much as I can say in terms of what the statute outlines in terms of an interchangeable product around the questions you're asking about substitution.

FDA would approve a product as either

biosimilar or interchangeable, but FDA doesn't have jurisdiction over pharmacy level substitutions. That's dictated by the state boards of pharmacy. There may be differences between the states about how it is that they deal with that, so it's not something that I can speak to specifically from the agency perspective about what may happen at the pharmacy level in different states because, again, that oversight is done by state boards of pharmacy, not the FDA.

DR. ARMSTRONG: Dr. Stroncek?

DR. STRONCEK: Throughout this presentation, it talks about patients. Well G-CSF is used extensively healthy donors, which aren't patients. And the risk benefit -- in my mind, the risk benefit ratio is quite a bit different for a patient using G-CSF in the therapeutic context versus a healthy donor donating stem cells for a sibling or for an unrelated person.

Has the FDA given any consideration to -- would these criteria be different if they're used in a donor type of situation, as opposed to a patient?

DR. CHRISTL: So in terms of the clinical data that would be generated, again we talk about the study designs and choosing the appropriate population. It's not just an adequately sensitive population to detect differences should they exist, but you have to, as you noted, look at how the product is used and make sure that there is sufficient information to be able to make a determination of whether there's an expectation of any clinically meaningful differences between the products. And that would include both safety and efficacy.

The agency and the sponsor would have to think about the necessary data. I don't want to get into too much about G-CSF because, again, we haven't heard the product-specific presentations, and mine is just really an outline of the general concepts.

But from a general standpoint, the agency would certainly consider in that totality of the evidence how the product is used and want to make sure that the complete data package was going to be answering questions about, are there clinically meaningful differences between the proposed product and the reference product, for which the biosimilar is seeking licensure.

DR. ARMSTRONG: Did that answer your question?

DR. STRONCEK: Yes.

DR. ARMSTRONG: I wondered if you could go into a little more detail about when a comparative clinical trial would be required, like what is the threshold of those residual uncertainties or differences that might trigger the requirement for a comparative trial?

DR. CHRISTL: Right. So again, there's going to be product-specific considerations, and it really depends on any differences that may be observed between the proposed product and the reference product coming out of that analytical similarity assessment, what we know about mechanism of action, are there certain quality attributes that are connected to PK, looking at the functional studies, receptor binding studies, other functional assays that are related to mechanism of action, and where you may or may not see those differences; and then looking at how best to evaluate the impact of those differences.

When we talked about the PK and PD studies, again, PK is generally expected, and PD if there's a relevant PD marker. So in the case of a product where you don't have a PD marker that's really going to give you information about the biological effect of the drug. And, again, whether or not it's on the mechanistic path of the mechanism of action or disease process, is this something that has to be considered for the product about really what we mean in terms of a relevant PD measure.

But if there isn't anything at all, it's more likely, in the context of determining residual uncertainty, of looking at the evaluation of clinically meaningful differences that you may need to look at conducting a comparative clinical study to answer those questions about residual uncertainty.

So there's a number of program and product specific considerations that would come in with any given program as to whether or not you -- or what clinical data that you need in terms of the entire package.

DR. ARMSTRONG: Dr. Fojo?

DR. FOJO: I had a question. The clinically meaningful differences, that's about as vague as it gets. I take it that's deliberate, right? We wouldn't approve something de novo for breast cancer or colon cancer based on "clinically meaningful differences." Is the thought here that, okay, this is -- the reference product has already been vetted extensively, aggressively, before it was ever approved. Now, we just want vagueness the rest of the way. So is that deliberate?

DR. CHRISTL: So again, the concept of biosimilarity is different than a standalone development program. And so we're looking at are there clinically meaningful differences between the proposed product and the reference product in terms of safety, purity, and potency of the product. And you can think of safety, purity, and potency in the same context as safety and efficacy. It's just the terminology that's used in the Public Health Service Act.

Again, a reference product would have to demonstrate safety and efficacy in adequate and well-controlled phase 3 trials; so those pivotal clinical trials. For the biosimilar, they're not demonstrating safety and effectiveness of their product in the standalone fashion. They're looking at demonstrating biosimilarity.

So that concept of no clinically meaningful differences between the products, again, in the context of safety and effectiveness, is intended that the biosimilar isn't expected to have a different clinical performance in safety and efficacy than that reference product.

DR. FOJO: So the answer is yes; it's deliberately vague.

DR. CHRISTL: Yes.

DR. FOJO: Okay.

DR. CHRISTL: Because the concept and the pathway is quite different.

DR. FOJO: Because I'm sure you could get disagreement on just about anything we ask the panel as to what is clinically meaningful here, about anything that would come up. Okay.

DR. ARMSTRONG: Dr. Hillard? I'm sorry. I forget to remind the panel, just restate your name before you --

DR. HILLARD: I was wondering -- it says that the interchangeable product may be substituted without intervention of the healthcare provider. Is it possible for the healthcare provider to do essentially what you do with generic drugs and say dispense as written or is it an automatic substitution?

DR. CHRISTL: Again, that's going to depend on the substitution laws in a given state, and the agency doesn't oversee that. That's dictated by the state boards of pharmacy.

DR. HILLARD: I'm sorry. Could you repeat that?

DR. CHRISTL: The concept of substitution is not something that the FDA oversees. Substitution is driven by activities at the state level. So that's overseen by the state boards of pharmacy. So it depends on what the substitution laws are in a given state.

DR. ARMSTRONG: Did that answer your question?

DR. HILLARD: Yes.

DR. ARMSTRONG: Okay. Other questions from the panel?

DR. COLE: Bernard Cole. I was curious about the choice for the numbers. I think it's slide 29, where you give an acceptance range of 80 to 125 percent for PK and PD outcomes. I was just curious where those numbers came from, and I would think an 80 percent ratio might be clinically meaningful. I'm wondering if you could explain.

DR. CHRISTL: Right. So the 80 to 125 are the bioequivalence criteria for generic drugs, and there was a lot of discussion around the sort of starting point of considering acceptance ranges. So we did look at what was done in other areas of the agency, not just for generic drugs, the other abbreviated approval pathway under the Food, Drug and Cosmetic Act, of looking at establishing bioequivalence.

So that 80 to 125 start point for consideration of the study design is in line with other abbreviated approval pathways in the agency. But again, you can scientifically justify the use of other ranges, and that may be a recommendation from the agency. It may be a proposal from a sponsor, depending on product-specific considerations about what could constitute a clinically meaningful difference in PK or PD for a given product.

So what we've articulated in draft guidance is that 80 to 125 is a general starting point, but it has to be considered within the context of a specific product in what could be considered a clinically meaningful difference.

DR. ARMSTRONG: Any other questions from the panel? Dr. Fojo?

DR. FOJO: So just to follow-up on that.

Tito Fojo. 80 to 125 is probably okay in a situation like this, where it's such a robust reference product, but you would recognize that in some cases 80 percent of the reference product might actually be suboptimal, right? So that's not written in stone, is what you just have said, right?

DR. CHRISTL: That is correct.

DR. FOJO: Okay. And then the other thing is, it would seem that an equivalence design is something that you would consider optimal. Because a lot of this is going to start turning into non-inferiority designs, which are, in my opinion, slippery slopes, with regards to the clinical trials.

DR. CHRISTL: Right. So in terms of the comparative clinical study, if one is necessary to be conducted to support the demonstration that there's no clinically meaningful differences, FDA has stated that typically an equivalence design would be used in such a trial design. But again, depending on the evidence that's been collected over time, product specific considerations about whether there are things like dose-related toxicities, things like that, other designs may be considered. But as a baseline expectation, FDA has articulated that for a comparative clinical study in a biosimilar development program, that typically the equivalence design would be expected.

DR. FOJO: Okay. Thank you.

DR. ARMSTRONG: Any other questions from the panel?

(No response.)

DR. ARMSTRONG: Thank you very much. We have a long agenda today, and fortunately we've moved ahead a little bit. So we are going to now start with the sponsor presentation.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will proceed now with the sponsor's presentation.

Applicant Presentation - Mark McCamish

DR. McCAMISH: Thank you, Dr. Armstrong. It's a pleasure for me to be here today to represent the Novartis group of companies, and Sandoz where Novartis' biosimilar activities are housed. In kicking off the sponsor presentation regarding our Zarxio biosimilar, which is the first biosimilar application to be entertained by an advisory committee.

We're also pleased that ODAC is that advisory committee. I can see from the discussions thus far, we'll have a robust discussion later, and I'm actually looking forward to that, as well as learning from you how we could present our information better, because this is a unique concept as you've already seen.

Along with this, let me just step back prior to our formal presentation and give you a little bit of information about our journey down the pathway of biosimilar development because we have all had to learn the differences and have a paradigm shift in terms of development of a biosimilar compared to novel drug development.

My background is fairly typical for a physician in the field. I'm a physician scientist. I'm double-boarded in the U.S. I had an academic appointment for about 10 years, first at University of California in the Division of Clinical Nutrition and Metabolism, and then at the Ohio State University in the Division of Endocrine Metabolism.

I've had two and a half decades of experience in industry and pharmaceutical research and development that's been primarily focused on biologics and the development of novel compounds.

I developed a passion for biosimilars based on personal experiences. My wife was diagnosed with ankylosing spondylitis about 30 years ago. This is a progressive inflammatory disease that can be treated now by an anti-TNF biologic. Now, despite having this disease with systemic manifestations and despite being in very good healthcare situations, both in the West Coast, East Coast, and now in Europe, my wife has not qualified for treatment with an anti-TNF because of the cost of that treatment.

So we've personally experienced patient access issues in our family, and this has given me a passion for really addressing access issues through development of biosimilars. And this has allowed me to bring that passion to Sandoz, and it's been a fabulous experience to join Sandoz where we've had so much experience in the biologics field.

It dates back to the 1940s when Sandoz developed fermentation capabilities for the production of anti-infectives, and then transitioned in the 80s to the development of recombinant technology, where we developed the first recombinant protein that was marketed in Europe. And then in the 90s we've also transitioned to the development of biosimilars, and that technology has allowed us to really be pioneers in the field of biosimilars, to learn this paradigm shift between the difference of developing a novel drug and developing a biosimilar.

We've also developed 20 to 25 different biologics for Novartis, for Sandoz, and for other biologic sponsors as a contract manufacturing organization. So it puts us in a unique experience in this, and we have been the pioneer in biosimilars as we've launched the first biosimilar in a highly regulated market in the world; first biosimilar in Europe; first biosimilar in Japan; and now, first biosimilar to be considered in the U.S.

So with that, we're really looking forward to this discussion and bring the experience we've had in this transition from developing a novel drug to a biosimilar.

So our presentation is outlined here, and this also follows along with the process of developing a biosimilar as outlined by Dr. Christl, wherein we will present on the analytical demonstration of biosimilarity. This will be presented by Hansjoerg Toll.

Dr. Toll is actually replacing Joerg Windisch, who is our chief science officer who is ill and could not be here today. So I appreciate Dr. Toll stepping in.

This will be followed by a presentation by Dr. Sigrid Balser on the clinical package. This will also be followed then by a brief presentation by Dr. Louis Weiner, who is professor and director of Lombardi Comprehensive Cancer Center and an expert in oncology and emphasizes research looking at targeted approaches to enhance the patient's immune system through the use of monoclonal antibodies to address various cancer needs. Then I will follow with a synopsis of the review of the data. Keep in mind that we will just be presenting high-level data here to give you an idea of the overall package that was submitted to the agency.

We have additional external consultants here that represent, really, the best in the oncology area, including Dr. Kimberly Blackwell, who's professor of medicine and really a breast cancer specialist from Duke University Medical Center. She's also a member of our DSMB, as well as an author in the publication for our pivotal trial.

Then Paul Cornes, who's a clinical oncologist from Bristol Hematology and Oncology Center in the U.K. He has perhaps the greatest experience with biosimilars overall, and with specifically with this filgrastim product in Europe, as well as been affiliated with many postmarketing activities in Europe.

Then Dr. Nadia Harbeck, who's a professor of medicine at the University of Munich and is the chair of our Data Safety Monitoring Committee, and also an international expert in breast cancer, including being a member of the St. Gallen's International expert consensus panel.

I wanted to mention a little bit regarding the evolution of the concept of sameness as it applies to biosimilarity, and both Dr. Christl mentioned this, as well as other activities. What I wanted to backup with a little bit is to look at the concept of sameness.

As you know, generic molecules were introduced in the '80s, and the concept of sameness was pretty straightforward there because you could produce an exact copy of the generic molecule because it was chemically synthesized. So this view of identical and having an identical copy was easy to understand at that point in time, and therefore, showing this sameness was fairly straightforward.

However, there are also complex generics, and I'm using enoxaparin as an example. Enoxaparin is a mixture of varying lengths of low molecular weight heparins, so it's impossible to show identicalness if you're producing a generic copy of that complex molecule.

Because of that, FDA developed five principles focused on proving sameness with a complex product. This happened to be a biologic. And this complex product was evaluated based on these five principles, which included analytical characterization of the mixture of the molecular entities forming this product and had to make a judgment call on the sameness of this mixture. And it allows for that evaluation of sameness based on data presented to them.

Comparability is another concept whereby a biologic company, whether it be Novartis or others, where they have to increase the manufacturing capacity for a biologics for patients that requires a manufacturing change. Regulatory authorities have to make a judgment on whether the pre-manufacturing change product is essentially the same as the post-manufacturing change product; so it is this evaluation of sameness, called comparability in a regulatory sense, that every manufacturer has to do when evaluating change in manufacturing processes.

This comparability has been going on for about two decades now, so regulatory authorities are familiar with the approach that's taken. Biosimilarity is kind of a culmination of the learnings of these activities, starting in 2004 in Europe and 2010 in the U.S. with the passage of the BPCIA.

In this situation, it's based on the terminology "highly similar," and the focus is on developing a product that's highly similar to the reference product in using a U.S. reference product here, based on an evolution of this concept of sameness, so that it's not totally unique to regulatory authorities in the evaluation of biosimilarity.

If I can go to the next slide, please, this slide outlines the biosimilar development. In the upper left-hand box, we illustrate the 351(a) approach, which is the traditional biologic approach.

At the bottom left, we outline 351(k). In this situation, the 351(a), as you're aware, you use analytics to describe your product. You're not comparing it to an existing product. And all of the lines leading out from that box represent the clinical data required to show safety and efficacy of the original product in multiple indications. And the bulk of the data that a clinician is used to evaluating is the clinical trial data around phase 3's for each of those indications.

You can see the dark arrows going between these two boxes, representing biosimilar concept as Dr. Woodcock introduced, requires this paradigm shift whereby the biosimilar development concept is focused on showing comparability, showing high similarity to the reference product; in this case using analytics to establish a high degree of similarity, including functional studies. And then the clinical trials that are utilized as outlined by these arrows focus on PK/PD, immunogenicity, and then a confirmatory trial. And that trial is used to confirm the similarity that's been established analytically as well as functionally. So it is a paradigm shift in terms of development of a biosimilar product.

Zarxio is a proposed biosimilar to the U.S. reference product Neupogen, or filgrastim. It is a recombinant G-CSF. It was first approved -- our product, Zarxio, was first approved in Europe in 2009. And in Europe, the brand name Zarxio is with a Z. In the U.S., the proposed brand name is Xarxio with an X.

Since approval in Europe as a biosimilar, we've become the market leader, volume leader, in Europe, and have over 7 and a half million days of experience with this product. Because the product has expanded in terms of use, and expanded the filgrastim use overall, we have also had to scale up manufacturing to produce more of this product for Europe. And this scale-up has happened since

2004, up until our application with the agency.

As you saw in the briefing books, both ours and FDA, we had to provide comparability data for our product showing that the product used in 2004 for clinical trials was essentially the same or comparable to the product that we're using today, as well as our high similarity determinations between our product and the reference product.

The dose route of administration indications for the proposed biosimilar, Zarxio, are the same as the indications for Neupogen here in the U.S. Outlined here for cancer patients receiving myelosuppressive chemotherapy, AML, cancer patients receiving BMT, and then patients undergoing peripheral blood progenitor cell collection in therapy, and patients with severe chronic neutropenia. The only differences between the indications in the U.S. and Europe, essentially, is the addition of HIV-associated neutropenia in Europe.

The development program will follow along the concepts outlined by Dr. Woodcock and by

Dr. Christl, where we'll focus on a battery of structural and functional analyses that Hansjoerg Toll will present; the nonclinical, which included five animal studies to assess PK toxicokinetics and local tolerance; and then the clinical, which is confirmatory studies, including the one pivotal PK/PD study, several other PK/PD studies that were used in our European approval that were submitted as supportive, and then the confirmatory safety and efficacy study in breast cancer patients.

I have three slides that simply go through the same tables that were provided to you in the briefing book that just document the package that we've submitted and how it essentially fulfills the statute language and the requirements as we understand them. Statutes refer to the single reference product and we have compared this to the single U.S. reference product.

It includes analytical data, demonstrating Zarxio is highly similar. We have five animal studies that assess the PD as well as toxicity and toxicokinetics, again consistent with the statute language.

In addition, if we can go to the next slide, clinical studies, we have relevant clinical data that were collected in 174 healthy volunteers and 388 breast cancer patients receiving this product in comparison to the reference. The mechanism of action is similar across all indications, and we address that as part of the statute language.

In addition, regarding the conditions of use, I've already mentioned that we're seeking the same conditions of use as the comparator, Neupogen. And then the route of administration is the same as the comparator as well. So this documents that we're meeting the statutes as we understand them.

I'd like to now go ahead and introduce the remainder of the sponsor presentations, to start out with Dr. Toll, who will speak about the analytical demonstration of biosimilarity.

Applicant Presentation - Hansjoerg Toll

DR. TOLL: Thank you, Dr. McCamish. It's a great honor for me to be here today to walk you through the analytical part of our presentation and to show you how we were able to demonstrate that Zarxio and Neupogen are highly similar products.

I would like to start to show you the complexity of filgrastim. Filgrastim is a biologic, and it's more complex than a small molecule chemical entity. But within biologics, we have different complexities, and filgrastim is a relatively simple biologic.

You can see here a comparison between filgrastim and other biological class, which is more complex than monoclonal antibody. Now, what makes filgrastim relatively simple? The fact that the protein is non-glycosylated. So we have a protein where no glycans are attached, and therefore we have one single main substance.

Compared to this, monoclonal antibodies are glycoproteins, and therefore, the active variant of the monoclonal antibodies is a mixture of variants. In addition, filgrastim is a rather small protein. It consists of one chain. It has 175 amino acids, and it has the molecular size of 18,800 dalton. And you can see on the slide that the monoclonal antibody is much more complex. It consists of 4 chains, it has more than 1,000 amino acids, and it has a molecular size, depending on the molecule, between 140 and 150,000 dalton.

Now, this relative comparison helps us when it comes to the characterization of the protein because filgrastim is easier to characterize than a monoclonal antibody.

In order to be able to develop a highly similar biosimilar, it's important to understand the development target. And the development target is the reference product variability, and there we concentrate especially on the critical quality attributes.

How can we find out the reference product variability? We have to analyze the originator to understand this variability. Once we have understood the variability, we can start with the development activities, starting from the recombinant cell line development, followed by the bioprocess and purification development and last but not least, the drug product development.

You can imagine this is a quite iterative process. There is a lot of interaction between analytics and process development, and it is necessary to evaluate each process step; in total, over 20 process steps.

If the result we are obtaining delivers us at the end the desired product, which is a highly similar product to the originator -- and sometimes it happens that you have to go back a step. You have to re-evaluate your process steps, and you have to just change your process parameters to really guarantee at the end that you have a highly similar product.

I spoke about the analysis of the reference product before we started development. We don't do this only before we start the development, but we do this over the whole development period because we have to know the variability of the originator product over the years, and we have to compare at the end of our development our product to the originator product. In this case, Zarxio to Neupogen.

Due to this fact, we have analyzed over 80 batches of Neupogen in a time frame of 10 years. So this gives us a very good understanding of the originator drug, a very good understanding of the variability of Neupogen with regard to the product variance.

Understanding the originator variability is important. The next step, which is really important to be able to do a systematical development of the biosimilar, is understanding the mode of action of the protein.

Filgrastim exerts its biological activity by the receptor activation, which then activates the mode of action, which can be, for example, the cell proliferation. Binding to the receptor is key for the mode of action. Once we have understood this, we can think about which quality attributes are relevant for this binding. And we assess all our quality attributes towards efficacy, so binding to the receptor, but we take also into account safety and immunogenicity aspects.

In this slide, you can see the main outcome of this critical quality assessment. You can see on the left, the quality attributes; then you can see the criticality we assessed of these quality attributes. So in red and orange, quality attributes with very high and high criticality, and in green, quality attributes with low criticality.

Then you can see for which parameter these quality attributes are relevant. Are they relevant for efficacy? Are they relevant for safety? Are they relevant for immunogenicity? Or, are they relevant for all three of them. And on the right, you can see the analytical method, which can be used to analyze the quality attribute.

I just would like to highlight three quality attributes to explain you a little better how we are doing this. I would like to start with the amino acid sequence, which has a very high criticality. So the biosimilar drug and the originator drug -- in our case, Zarxio and Neupogen -- have to have the same amino acid sequence because a wrong amino acid sequence may end up in a wrong folding of the protein, which then has an impact on efficacy, if the drug doesn't bind to the receptor, safety and immunogenicity.

Product-related variants are very high importance if they have an impact. For example, the high molecular weight variance, they are known to be potentially immunogenic, and therefore, they are ranked high in criticality. Or in the case of filgrastim, the oxidized variants, it is known from the literature, and we also have proven this by our own experiments, that oxidized variants are lower in their biological activity, and therefore they are ranked high in criticality.

You can see already the analytical methods on the right of the slide. So it's essential to have sensitive analytical tools in our hands to be able to analyze these quality attributes during the development and to be able to do a thorough comparability exercise at the end of the development, a thorough biosimilarity exercise with sensitive methods.

Here, it really helps us that the analytical science improved significantly over the last

20 years. So there are analytical methods available to assess, for example, the higher order structure, like 2D nuclear magnetic resonance spectroscopy, which have not been here to this extent two decades ago.

Or another example, I would like to show you a slide that's from Tony Mire-Sluis, who was before at FDA, where you can see that the sensitivity of analytical methods, in this case mass spectrometry, which is the method which is the most relevant method to analyze product-related variants -- you can see here that the sensitivity increased dramatically over the last decade, so we have an increase in sensitivity of 10-million fold.

This now allows us to analyze and to follow product-related variants in the extreme sensitive way compared to, for example, 25 years ago.

During the next slides, I would like to show you head-to-head comparison data between Zarxio and Neupogen, and I would like to focus on the critical quality attributes. And we will start with the structure with the folding of the protein.

A protein is defined by its primary structure, which is essentially the amino acid sequence; by its secondary structure, which are structural elements like alpha helix or beta sheets; and then by its tertiary structure, which is the folding of the secondary structure in the three-dimensional space. For all of the structural elements we have analytical methods in place to analyze them and to compare them to the originator.

The primary structure can be assessed by a combination of analytical methods like Edman sequencing, peptide mapping, mass spectrometry, and mass spectrometric sequencing, and amino acid analysis. And I would like to show you a comparison of our peptide map data, so of the peptide map data between Zarxio and Neupogen, because this is the most relevant method when it comes to the assessment of the amino acid sequence.

When doing a peptide mapping, we are digesting. We are cutting the protein into smaller peptides. You can see this by the red signs. And we then separate the generated peptides according to the hydrophobicity by use of reversed-phase high-performance liquid chromatography, which is also known as RP-HPLC. Subsequently, we can sequence the separate peptides in the mass spectrometer.

In this slide, you can see a comparison of the peptide map illusion between Neupogen and Zarxio. Now, you can directly see that both products first deliver the same peptides and that the retention time of both products is highly similar. So this is already a strong indication that both products have the same primary sequence.

In addition, the sequencing within the mass spec delivers not only highly similar primary structure, but in this case, identical primary structure between Zarxio and Neupogen.

The next level in assessing the protein structure is the analysis of the high order structures. This is the secondary structure and the tertiary structure. For this, we are using methods like circular dichroism spectroscopy and the already mentioned 2D-NMR.

Before showing the comparison of CD data, I would like to shortly explain the method. Circular dichroism spectroscopy makes use of the fact that left and right polarized light is absorbed differently by the secondary structural elements. So you obtain different spectra when you analyze alpha-helical product compared to a product, which is mainly composed by data sheets or is even unfolded.

I would like to draw your attention to the alpha-helical spectra, to the right spectra, because filgrastim is an alpha-helical product. And here you can see the comparison between Zarxio and Neupogen. So it's an overlay of 6 Zarxio batches and 6 Neupogen batches, and the spectra are superimposable. This first shows that both products have a highly similar secondary structure, but it also shows that both products are mainly composed by alpha-helical components.

The last step in assessing the structure is the analysis of the tertiary structure, of the three-dimensional structure, and we do this by use of 2D-NMR. And before showing you the comparative data of 2D-NMR, I would like to discuss the sensitivity of these methods with regards to changes in the folding of the protein.

These are data published by scientists from the FDA together with scientists from Health Canada and from the European Standard Institute, NIPSE [ph]. And what they did, they compared a related protein to G-CSF, GMCSF, one time the wild-type, and one time they exchanged one amino acid -- in fact, it's only a change of two atoms -- and compared these two proteins.

What you can see on the left is the 2D-NMR spectra. Here you can see the relation between hydrogen and nitrogen points. And what this shows you is for each dot, a signal of the amino acids in the three-dimensional space.

Now, when you have a change in the structure, the signal will move in the spectrum, and you will detect it. And you can see that by comparing the wild type with the protein, where the amino acid exchange happened, amino acids are changing the position in the three-dimensional space, and changes in the folding can be sensitively analyzed with this method.

Here you can see the overlay between Zarxio and Neupogen, superimposable spectra. Neupogen is shown as an orange dot, and Zarxio has the blue halo around the orange dot. And everywhere where we have an orange dot, you can see also the blue halo. So this analytical method really shows that Neupogen and Zarxio have highly similar higher order structure.

The next step in assessing if both products are highly similar is the comparison of product-related variants. And I have mentioned at the beginning of my talk two product-related variants, and I would like to start with the oxidized variants, where we know that the biological activity is lower compared to the main variant.

Oxidized variants differ in hydrophobicity from the main variant of filgrastim, and we can use this by analyzing oxidized variants with RP-HPLC.

Here you can see a separation of the intact molecule, and what you can see at a glance is that the intact -- so the separation of this intact molecule, the separation of Zarxio, shows a very pure protein. So the product-related variants are of very, very low concentration. So you really have to zoom in to see the product-related variants.

Now dimension oxidized variants are lower in hydrophobicity, dilute on the left of the main peak. On the right of the main peak, you see dilution of deamidated/norleucine variants, product-related variants, where we know that they don't have any impact on efficacy.

When comparing now Zarxio to Neupogen, I would like to draw your attention to the left side of the chromatograms. You can see here that the oxidized variants are highly similar. This is due to the fact that, first, we have the same oxidized variants between Neupogen and Zarxio, but also, the quantity of these oxidized variants is highly similar, taking into account the very low level of oxidized variants present in both products.

A second important product-related variant is the high molecular weight variants. So these are dimers, oligomers, and aggregates. And we can analyze these variants by use of size exclusion chromatography, which separates the protein according to its size. And I would like to show you -- directly zoom into the chromatogram, And what you can see here is hardly a peak because both products are highly pure with regard to these variants, which are of high importance due to its potential immunogenicity.

We have proven these results with an orthogonal method, with the analytical ultracentrifugation, where we also obtained highly similar results between Neupogen and Zarxio.

We have seen that Neupogen and Zarxio have the same structure, and they have the same amount and variance of product-related variants, which have high criticality. Now the question is, do products also bind the same way to the G-CSF receptor? And to find this out, we performed surface plasmon resonance spectroscopy, also known as Biacore. And you can see here, the overlay of 6 Neupogen batches. And in the sensogram, you can see that both products have the same association and dissociation behavior to the G-CSF receptor.

Also, the numerical evaluation of this method shows highly similar results for the association constant K-on, for the dissociation constant K-off, and also for the affinity constant, taking into account the variability of the method.

To finally prove that both products have also highly similar biological activity, we need to perform an in vitro bioassay, and you can see here the results of the in vitro bioassay. On the left of the slide, you can find an explanation how this assay works.

We have murine leukemia cells where we add filgrastim, and by adding filgrastim, cell proliferation happens. We add filgrastim in different concentrations, so we are able to obtain a dose-response curve. So you can the dose-response curve on the right of the slide. By comparing the dose-response curve of the product to a reference, we are able to calculate the biological activity of the sample. This bioassay is in accordance to the bioassay in the USP monograph for filgrastim.

Taking a look now to the numerical results, we see that the biological activities are highly similar. Zarxio shows biological activity in the range of 1.0 to 1.1 units per milligram times 10 to the 8th. Neupogen shows biological activity in the range of 1.0 to 1.2 units per milligram times 10 to the 8th. These values are well within the definition of Neupogen, in the Neupogen product information, which is in the range of 0.4 to 1.6 units per milligram times 10 to the 8th.

After having seen that the products have the same structure, they have the same level of product-related variants and they have the same binding to the receptor and the same biological activity, it is of high importance that both products have also the same content.

You can see here the comparison of the

content data between Zarxio and Neupogen, and I would like to draw your attention to the Y-axis, where you can see that all levels are in the range of 95 to 105 percent to the declared content, which is a well-accepted range in the biotechnology field.

Taking a closer look, you can see that all products show the main population around 100 percent, and also by doing equivalence testing, we were able to show that Zarxio and Neupogen have equivalent content.

For completeness, I would like to show you the comparison of the formulation between Zarxio and Neupogen. The formulation is highly similar. We have the same solvent, the same surfactant, the same tonifying agent. The only small difference is that we use a buffer with a slightly higher pH.

I have shown you that Zarxio and Neupogen are highly similar with regard to their structure; primary structure, secondary structure, and tertiary structure. Both products are highly similar with regard to their heterogeneity, taking into account especially the critical quality attributes. They are highly similar with regard to their function and their pharmaceutical properties. And this means that we have two highly similar products, Neupogen and Zarxio.

With this, I'm at the end of my part, and I would like to thank you for attention and to hand over to Dr. Balser for the clinical part of the presentation.

Applicant Presentation - Sigrid Balser

DR. BALSER: Thank you Dr. Toll for the analytical presentation, and it's now my great pleasure to walk you through the clinical development program that we have performed for our product.

Before we dive into the details, I would like to go back to what Dr. Christl and Dr. Woodcock had said before, that when we look at the clinical development program for a biosimilar, there are different things that we have to consider as compared to an originator development.

For once, we don't look at the clinical

development program as an isolated piece, but it is to be seen in the conjunction with all the analytical work that has been done, and Dr. Toll has just shown the high degree of similarity that we have on an analytical level.

So the clinical development program is the final step to confirming the similarity in a population where the product will be used later on and having a sensitive setting there. And in particular, the sensitive setting and the goal of establishing biosimilarity also leads to different considerations when we choose the populations, the endpoints. And you will see this in the clinical program that we have conducted.

In this slide, you have the overview of all the studies that went into our file, and you see this is a very comprehensive and quite extensive package actually. And it is more, I would assume, than you would expect, based on what you have heard before from Dr. Christl. But this is due to the fact that our development program for the U.S. was built upon the previous development program that we had conducted for Europe.

The two studies that you see on top in the red box are the two studies, which were specifically conducted for our U.S. development program. You see it consists of a study in healthy volunteers, a PK/PD study, and we also do have a comparative study in breast cancer patients.

In both these studies, we have the U.S. reference product, Neupogen, as the reference product. And this is complemented by a set of additional healthy volunteer PK/PD studies, as said, which were a part of the European development program where we have the European reference product as well, and Neupogen as the reference product.

But the analytical data that we have generated shows that both the U.S. and the European Neupogen product are essentially the same, so all of these studies are relevant for the evaluation of biosimilarity in this context.

What you can see also is that these healthy volunteer PK/PD studies cover a wide range of doses. We have doses between 1 microgram per kilogram, up to 10 micrograms per kilogram. We have subcutaneous, and we have intravenous administration. And you will see this later on. We also have single-dose as well as multiple-dose applications.

As part of our European package, we also had a single arm study in breast cancer patients to look at the safety and immunogenicity since the European package was primarily built on this extensive PK/PD comparability that we have performed in healthy volunteers.

Finally, the package also contains a study, which is currently still ongoing. It's a study in healthy donors where we look at the efficacy and safety in this particular setting.

On the right-hand side, what you see are essentially the parameters and the objectives in the various studies. The healthy volunteer studies all had a primary component in terms of looking at PK and PD equivalence, but of course we always gather safety and immunogenicity data in these studies.

For the breast cancer studies, there was of course more focus in terms of efficacy, but also here, we have safety and immunogenicity being evaluated in a comparative setting and in study 302, which was the comparative study in breast cancer patients for our U.S. file that also included a small PK substudy.

So you see that this is quite a comprehensive collection of studies, and I will only be able to go into some of the high-level results. And we will primarily focus on the PK/PD study 109, which is the top one, as well as the breast cancer study, which was the 302 study. And I will show you more details on those on the following slides.

So we'll start out with the PK/PD study, and we heard that this is kind of the first step in confirming the biosimilarity. This study was conducted in healthy volunteers to establish pharmacokinetic as well as pharmacodynamic equivalence.

Before we go into the design and actually the results of this study, I would like to step back and say, why is this a good setting to establish biosimilarity? And we have heard before that we are looking for a very sensitive setting so that in case there are any differences, we are able to pick them up.

The advantage with filgrastim is if we look at the clinically relevant markers, which is the absolute neutrophil count for the neutropenic indications and the CD34 positive cells for the mobilization indications, we have the same mode of action independent of the population. And so we can measure these relevant markers also in the healthy volunteers.

Here, the big advantage is actually that the bone marrow of these healthy volunteers is fully responsive, so we can very well pick up a response in these PD markers.

Of course with any healthy volunteer study, you do have the advantage of having less confounding factors, and we are able, due to the short half-life of this product, to conduct these studies in a crossover design, which reduces the variability and therefore also increases the sensitivity of such a study.

The final point also is healthy volunteers are full immunocompetent, so we are able to pick up any potential immunogenicity, should it exist. So these are the general considerations why a healthy volunteer study is, indeed, a good setting to establish biosimilarity.

Now looking at more details on the study design, as said, it is a crossover design that we have chosen for the healthy volunteer study. And in this particular study, we used a single dose in each period of 10 microgram per kilogram and had this administered subcutaneously.

So on day 1, patients were randomized to one of the two treatment sequences, either starting off with Zarxio in the first period, and then crossing over to Neupogen in the second or the other way around. The single-dose administration at the start of each period was followed by a blood sampling period of 15 days to gather the relevant samples for PK and the PD evaluations. In between the two applications of each period, we had an overall washout period of 28 days.

If we look at the objectives of the study, as said, the primary objective was to establish PK and PD equivalence. And for the PK and PD equivalence, we had set this up in a hierarchal testing structure so that in the first step we were looking at PD equivalence in terms of the ANC response as measured by the maximum effect, Emax, and the area under the effect curve, the AUC.

If this test was successful, then in the next step, PK equivalence was to be assessed in terms of the usual parameters, Cmax, the maximum concentration, and AUC being the area under the concentration curve. And as we had heard before by Dr. Christl, the margins that were used to establish or assess equivalence were the commonly used bioequivalence margins of 80 to 125 percent.

With respect to PK, we actually used a 90 percent confidence interval as just presented before, and for PD, we actually took a more conservative approach by looking at the 95 percent confidence intervals, but both of them being compared to those margins between 80 and 125 percent.

In terms of the secondary objectives, the CD34 positive cell count is the other relevant marker, in particular, in the context when we think about mobilization indications. And of course, we have safety and immunogenicity as well as local tolerance also as the secondary objectives. And the design of the study, we should mention this, was discussed with FDA prior to the initiation of the study.

Now let me share with you some of the results. We'll start out with the PK results, which was one of the primary objectives of the study. And what you see here on the slide is on the left-hand side, the mean concentrations for Zarxio and Neupogen. Zarxio is always going to be depicted in blue, and Neupogen is always going to be depicted in red. This is on this slide and all of the following slides.

You see reasonably similar profiles on the mean concentrations and the standard deviations that we have here. And if we look at the right-hand side, what you see here is the results of the statistical evaluation to assess bioequivalence.

For both the parameters AUC as well as Cmax, you see the point estimates when we look at the ratio of these parameters between Zarxio and Neupogen together with the corresponding 90 percent confidence intervals. And whenever these point estimates together with the confidence intervals are within these pre-defined boundaries of 80 to 125 percent, which we have depicted here, the green lines, then we can conclude PK bioequivalence.

What you can clearly see is the ratios, the confidence intervals, are well within the margins, and so the study has established PK bioequivalence between Zarxio and Neupogen.

Now let's look at the PD results. And here first looking at the AUC response, on the left-hand side, similarly you see the mean concentration profiles. And they're highly superimposable; they're hard to tell apart. We have a nearly identical response in terms of the ANC cell counts.

If you look at the right-hand side, the corresponding statistical evaluation for equivalence, we have ratios between the two groups, Zarxio and Neupogen, very close to a 100 percent. And the confidence intervals, again in this case, we took the more conservative approach looking at 95 percent confidence intervals. They're also well within the predefined boundaries, clearly showing equivalence between Zarxio and Neupogen in terms of the ANC response.

We have a similar picture when we look at the CD34 positive cell response, even though that study wasn't of power to show equivalence in terms of this marker, we're of course still interested in the similarity of the response for the two products.

Again, if we look at the mean concentration profiles, they're highly similar between the two products. And also then, if we look at the ratios and corresponding confidence intervals, we again see that these fall within the usual bioequivalence margins of 80 to 125 percent, also showing an equivalent response for this marker between Zarxio and Neupogen.

Now these are the results for the single PK/PD study that we have conducted with the U.S. reference product, but I would like to put this also in context to the other healthy volunteer studies that we have performed.

In this slide -- and I have to admit, it is a little bit of a busy slide, but I'll try to walk you through the slide. On this slide, we have the pharmacodynamic response profiles of all the studies that we have conducted. On the left-hand side, we have the ANC profiles in healthy volunteers. And the top part of this is from the single-dose studies, and the lower part from the multiple-dose studies.

If we look at first at the single-dose studies, you see a nice dose-response relationship.

And for each of the dose levels studied, we see highly similar profiles. And the doses studied, in the single-dose setting, from lower to the upper part, are 1 microgram per kilogram administration as the lowest curve; the medium or the middle one is from a 5 microgram per kilogram administration, administered IV; and the top one is actually from the study that I had just shown previously, using a 10 microgram per kilogram dose.

If we turn to the lower part of the slide, we have the multiple-dose studies. And here we look at the ANC counts on the left-hand side and the CD34 positive profile on the right-hand side. And for these multiple-dose studies, all of them are crossover studies, but here we had seven applications per period.

The dose levels that we had studied were 2.5, 5, and 10 microgram per kilogram. And again, what you see is you see a very good dose-response relationship for all the three doses studied, and you see a nearly identical response at each of those dose levels between Zarxio and Neupogen.

So overall, we have a high similarity also in terms of the PD response for both the relevant markers, ANC representing the neutropenic indication, as well as CD34 positives, which are relevant for the mobilization indications.

When I say we have a very nice dose-response relationship, this is depicted on the next slide, that there is a good dose-response relationship, and it is very similar between the two products.

On this slide, I have focused only on the multiple-dose studies, but we have a similar picture if we look at single-dose studies. Again, we have two columns, the left one representing the absolute neutrophil count, and on the right-hand side, the CD34 positive cell counts.

Looking at the multiple-dose studies, as said, we had doses of 2.5, 5, and 10, and we see a clear dose-response relationship, which is similar for both products, and it also shows you that the comparative assessments that we have done were in the sensitive setting, not in the saturation setting.

So the overall set of PK and PD studies that we have conducted clearly shows a high degree of similarity in terms of PK as well as PD response as measured by ANC, as well as CD34 positive cells.

So this is somewhat of a snapshot of our PK and PD data, and now I would like to move on to our comparative phase 3 study.

So as said, the comparative study in breast cancer patients, which we have actually conducted, was the final step to confirm the similarity between Zarxio and Neupogen, building upon the analytical evidence, as well as the data that we have seen in the PK and PD studies.

Similarly to what I had before when we look at why did we choose the setting that we have chosen, in terms of healthy volunteers for the PK/PD assessments, we have a similar assessment on why did we choose the population as breast cancer patients and the corresponding myelosuppressive chemotherapy for this trial, which was chosen to be TAC, and why did we choose the primary endpoint that we have chosen, namely the duration of severe neutropenia.

If you remember, we have to find a sensitive setting to establish biosimilarity, but also that gives us a chance to pick up differences should they exist. And in this particular case, if you look at a breast cancer population, we have a relatively homogeneous population. And the treatment guidelines support the use of TAC chemotherapy as the standard curative treatment in early breast cancer patients.

The issue with the TAC chemotherapy regimen is that it has a substantial hematological toxicity with a large number of patients experiencing severe neutropenia, if not given G-CSF prophylaxis. And so the treatment guidelines actually require the use of G-CSF as primary prophylaxis. And in this particular setting, G-CSF has been proven to be efficacious by reducing the duration of severe neutropenia, and therefore also reducing the risk for febrile neutropenia or other complications.

Actually, this model, if I call it a model, has become a well-established one to compare products of the G-CSF class. The duration of severe neutropenia as a primary objective is an objective measure for the treatment response, and we have seen similar designs of studies, for example, in the pivotal trial for Neulasta. And also, for this study, we had discussions beforehand with FDA in terms of the appropriateness of the setting.

This again is the background information on why we have chosen a study in breast cancer patients with chemotherapy of TAC. The primary objective in the study was then to assess non-inferiority in terms of the mean duration of severe neutropenia in a cycle 1 of breast cancer patients receiving TAC chemotherapy. And non-inferiority in this sense -- and this was brought up earlier -- was deemed appropriate.

Looking at all the data that had been gathered beforehand, we have a high degree of similarity. From an analytical perspective, we have established PK and PD equivalence in the healthy volunteer setting. So the objective was to rule out inferiority in terms of efficacy, so the non-inferiority assessment was deemed appropriate.

In the study, we had a number of secondary objectives, which would also look familiar to you in this particular setting. We have the incidence of febrile neutropenia. We're looking at the number of days of fever and the depth of the nadir, as well as the time to ANC recovery in cycle 1. We look at the frequency of infections, as well as the incidence and duration of hospitalizations due to febrile neutropenia.

Part of the safety endpoints, also the usually ones, we're looking at the incidence, occurrence, and severity of any adverse events and of serious adverse events. We're looking at local tolerability and systemic tolerance. And importantly, we of course look at the immunogenicity and potential formation of antibodies.

Now, if we look into the design of the study, we said the patients received TAC chemotherapy in total over 6 cycles, and this is what essentially each cycle looked like.

On the first day, the TAC chemotherapy was applied using the approved label dose for docetaxel, doxorubicin, and cyclophosphamide. And then starting on day 2, G-CSF support was provided either by Zarxio or using Neupogen, and the treatment was performed with 5 microgram per kilogram per day until either the ANC has recovered to 10,000 or for, at most, 14 days. And then we have a short essentially treatment free period for the full cycle length of 21 days, and then afterwards the next cycle is initiated.

So this is what each of these cycles looks like, and the next slide then shows you the overall design of the study. And in this particular study, we had 218 patients included, and they were randomized into 4 arms. We have 2 arms, the top one and the lower one, where patients stayed continuously on their initial treatment being Zarxio or Neupogen. And the two middle arms started in switching part from cycle 2 onwards. The design of the study was chosen that way to also assess switching and subsequently interchangeability. But as said before, this is not part of this current submission.

So for the analysis, we will focus, first of all, on the cycle 1 data to assess the primary endpoint, and we will later on also look at the continuous arms when we look at safety across all the 6 cycles.

So if we look at the analysis for the first cycle, then of course we can combine the top 2 groups to get the overall -- the patients who were exposed to Zarxio and combine the lower 2 ones for all patients exposed to Neupogen. And for these two groups, we then assess the non-inferiority in terms of the duration of severe neutropenia, and the predefined margin for this was 1 day.

What I would like to briefly show you is the baseline characteristics of these patients as randomized in the first cycle, and you see that the two groups match up very nicely in terms of age, time since the initial diagnosis and the staging. And the majority of the patients received TAC in an adjuvant setting with around 58 percent, and the other 42 percent received TAC in the neoadjuvant setting. So we have a well-balanced group of patients in the two treatment arms.

Before we look at the results of the primary endpoint, I would like to show you the ANC profile, similarly to what we have seen before in the PK/PD studies.

The profiles that you see here is exactly what you would expect in this setting. You have an initial burst in the neutrophil counts, which is mainly driven by the chemotherapy. Afterwards you have a decrease in neutrophil count with an nadir around day 7 or day 8. And then you have the recovery driven by the treatment with G-CSF.

If you recall, the treatment was to be continued until the ANC count had recovered to about 10,000, which was the case for most of the patients by day 11. On the lower part of the slide, you see the number of patients, which are still on treatment at the specific days. And you see this decreases rather rapidly after day 11, and then we only have kind of a handful of patients still being treated at that point. But it's important to note that even in those patients, the ANC counts were well above what we would consider a critical level.

By the end of the cycle, day 21, which coincides then with the start of the next cycle, all the neutrophil counts had returned to the baseline levels in both groups, with similar baseline values then for the start of the next cycle. So for all the patients, the subsequent cycle could be started as planned.

So that's kind of the general picture what we have seen in terms of the ANC counts, and how does this translate for our primary endpoint? What you see on this slide are the results for the duration of severe neutropenia, which was our primary endpoint.

On the left-hand side in the box, you see the mean values for each of the two groups, and you see that the mean duration in the Zarxio group was 1.17 day, as compared to the Neupogen group with

1.2 days. So you have these estimates together with 95 percent confidence intervals. So essentially here, we already see that as no difference between the two groups in terms of the duration of severe neutropenia.

This also is then translated. If you look at the comparison, the statistical comparison, which is given on the right-hand side, if we look at the difference between the two, the point estimate is .04, so essentially there is a zero difference in terms of the duration of severe neutropenia.

As I had said before, the study was set up as a non-inferiority study, so the corresponding confidence interval, which we are looking at is a one-sided one, and the lower boundary of this confidence interval was minus .26, so roughly a quarter of a day, which is well above the predefined non-inferiority margin of minus 1 day.

What we had heard before is that, yes, commonly you would expect an equivalence assessment. So we have also provided here the results that you would see if you did an equivalence testing using a two-sided confidence interval and a 90 percent confidence level. And also, these data show that the data generated in the study actually is of course the conclusion of equivalence for the duration of severe neutropenia for Zarxio and Neupogen.

So these are the results for the primary endpoint, and this is complemented by the number of secondary endpoints, which I have split into the ones, which are more driven by the neutrophil count than maybe the more clinical endpoints like febrile neutropenia, hospitalizations, and the incidence of infections, and lastly, the fever episodes.

If you look at the point estimates in the two groups, if we start on the top one, the depth of the nadir as well as the time to the ANC recovery is quite similar between the two groups. And this is also depicted on the right-hand side where you have a graphical display of the comparison between the two groups.

You see that the point estimate for the

difference is close to zero, so there is no difference between the two groups, and the bars that you see are the corresponding 95 percent confidence intervals, also indicating that there is no significant difference between the groups for any of these parameters.

This holds true for those as said, which are mainly driven by ANC, like the nadir, and the time to recovery. But also, when we look at the incidence of febrile neutropenia, the incidence of hospitalizations due to febrile neutropenia, or also the incidence of infections, which are overall very low anyway, and there is no difference between the two groups. And we also see that the majority of the patients did not experience any fever episodes, and if so, they were at most a duration of two days for both groups.

So this showed you the similarity, the high degree of similarity in terms of the efficacy of the two products. Now we'd like to look also at the safety profile. And here we focus on those two groups, which were continuously treated with the same product over all six cycles.

What we have here is kind of an overall display in terms of the incidence of adverse events. First of all, almost all the patients experienced any adverse event, and if we look at the incidence for study drug-related adverse events or chemotherapy-related adverse events, those rates are also very similar between the two groups.

If we look at the serious adverse events in the lower part of the table, first of all, we see that the incidence overall was quite low, and none of the serious adverse events which were observed were attributed to either one of the two treatments.

So this is the general picture. If we now look into more detail on the type of events that were observed, this depicts the most frequent adverse events, meaning they were observed in 5 percent or more of the patients in either one of those treatment groups. And it is important to note this really is about all adverse events, which were observed in the study, not only the study drug-related or chemotherapy-related; just any adverse event.

On the right-hand side, there is again the graphical display when we compare the two products. And what you see there is the risk difference together with the 95 percent confidence intervals. And wherever you have the dot on the left side of the zero reference line, this indicates that there's a lower incidence in the Zarxio group; whenever you have the dot on the right-hand side, the incidence is lower in the Neupogen group.

If you look at the overall picture, it is quite balanced. There are a number of adverse events where the incidence is higher in the Zarxio group, and they're in other events where the incidence is higher in the Neupogen group. None of those have any significance in terms of the comparison, and so we have an overall very balanced picture in terms of the adverse events that were observed in the study.

So overall, this confirmatory study showed equivalence in terms of efficacy, and it also provided a similar safety profile for the two products.

Now I would like to touch on another topic, which of course is also very relevant, immunogenicity. And across the number of studies that we have performed, there was a large number of samples that had been tested, and there were no signs of immunogenicity in any of these samples, and this is summarized on the next slide.

I have divided the slide into two parts. Under the top one, we have the breast cancer patients; the lower part shows you the results of our healthy volunteer studies. If we start out with the breast cancer patient studies, the study 302 is the one, which I was just talking about, in which 214 patients were treated. The 301 study is the single arm study that was performed as part of the European package.

Overall, we see that we have close to 400 patients being treated either with Neupogen or Zarxio, and you see a large number of samples that have been taken.

The next two columns show the results of the immunogenicity testing. What is labeled here as RIP positive is a radioimmunoprecipitation assay, which tests for binding antibodies. And only in case if you do have binding antibodies, we would move on to have a neutralizing antibody test.

If you look at the results for these breast cancer patients, we see that there are no binding antibodies and so we also have no neutralizing antibody testing to be performed. In the lower part, if we look at the healthy volunteer studies, we have split this into the single-dose and the multiple-dose studies.

If I start with the multiple-dose studies, and we have talked about this before, this covered a range of doses from 2.5 to 10 microgram per kilogram with 7 applications per period. Although in these patients there were no binding antibodies detected, and so again, no neutralizing testing was necessary.

If we look at the single-dose study, there you see that we have three positive samples. And here this is important to note, the samples were positive in one single subject, and the subject was positive already prior to entry to the study. So we did have a positive signal even before the healthy volunteer was exposed to G-CSF. And during the course of the study, the titer did not change. There was no increase in signal, leading to the conclusion that the signal that we have may not even be attributed as a response to G-CSF.

So overall, there were no signs for immunogenicity in any of the patients and samples tested; neither patients being treated with Neupogen or Zarxio. And knowing the low immunogenic potential of Neupogen and what is known for the product, this is not a surprise, but it's more a confirmation that we also see no immunogenicity with our product.

Finally, we have all the clinical data, but as mentioned before, this product has been approved first in 2009. So we have quite some extensive postmarketing experience as well.

This is a summary of what has happened since

2009 when the product was first approved. By now, the product is approved in over 60 countries worldwide, and we have gathered more than 7.5 million patient days of exposure. And as mentioned before, it's currently actually the most prescribed daily filgrastim in Europe.

The safety of the product is monitored both in several postmarketing studies, as well as by the routine pharmacovigilance system, which we have in place, which also includes the periodic safety updates. Up to this point we have close to 4,000 patients included in our postmarketing studies which covered a wide range of indications, not only chemotherapy and used neutropenia in several cancer indications, but also stem cell mobilization and severe chronic neutropenia.

In none of these studies have we seen any signals for a potential difference in the safety profile as compared to Neupogen. The same is supported by the routine pharmacovigilance assessment. There are no cases of immunogenicity reported up to date, and this triggered no additional risk minimization activities, which are required beyond what is already in the product information, which is the same for all G-CSF class products. So in the daily routine, it also established and confirmed the safety and effectiveness of Zarxio.

When I said we have a large number of postmarketing studies conducted, I would like to draw your attention to one particular one, which is a study, which is still currently ongoing. It's a study in healthy stem cell donors. The primary objective of the study was to look at the long-term safety in this indication, but of course, we also generate data in terms of the effectiveness.

These donors in the study are treated with the labeled dose of 10 micrograms per kilogram per day, with the apheresis starting on day 5. And as common, the target for the mobilization is to have a harvest in the donor of at least 4 cells per kilogram of the recipient body weight.

Up to this point we have not seen any safety signals in the study as well, and so I would like to show you the results in terms of the effectiveness of the harvest, which is shown by the box plots on the right-hand side.

In the majority of the donors, one apheresis was sufficient to harvest a sufficient number of cells, and only in about 10 percent of the donors, a second apheresis was necessary. If you look at the box plot at the far right, that shows you the overall yield in all these donors. And you see that the lower bound, the minimum, is above the desired minimum yield of 4 cells per kilogram of the recipient.

So this confirmed the effectiveness of Zarxio in this particular setting. It kind of confirms also what we had seen previously in our PK/PD studies where we have seen a similar response in terms of the CD34 positive cell counts.

With this, I come to the conclusion and the overall summary of the human experience that we have to date with Zarxio. For once, if we look at this, we have clearly established PK equivalence in the healthy volunteer setting. When you look at the relevant markers, the absolute neutrophil count for neutropenic indications or the CD34 positive cell response, more relevant for the mobilization indications, we have shown equivalent for both.

We have seen equivalent responses across the different treatment regimens and dose levels in terms of ANC both in breast cancer patients as well as in healthy volunteers. The CD34 positive cell responses also were highly similar between the two products, and also the postmarketing study showed the proven effectiveness of the product.

So across all the indications studied, we see a very similar response profile as compared to what is known for Neupogen, and this is also confirmed by the postmarketing data that we have generated.

In terms of the safety of the product, the incidence and the nature of the adverse events that we have seen are similar between Zarxio and Neupogen, and they are what you would expect in the indications. There were no signs of immunogenicity up to this point, and no concerning or unexpected safety findings for Zarxio, neither in the clinical development program, nor in the postmarketing experience. All the data gathered establishes that there are no clinically meaningful differences between Zarxio and Neupogen.

With this, I would like to thank you for your attention and like to hand it over to Dr. Weiner to give his perspective on biosimilars and biosimilarity. Thank you.

Applicant Presentation – Louis Weiner

DR. WEINER: Thank you, Dr. Balser.

I'm pleased to be here this morning to discuss a clinical perspective on biosimilarity. My name is Louis Weiner. I'm director of the Georgetown Lombardi Comprehensive Cancer Center, chair of the Department of Oncology. I'm a medical oncologist with an interest in targeted therapies using antibodies and have an experience with antibody engineering as well.

I'm here because I believe that biosimilars offer enormous promise to reduce the cost and improve access to biologic agents for the treatment of cancer.

These are my conflicts of interest. Aside from my consultancy with Sandoz, you'll see that my other activities are related to my interests in immunotherapy and antibody engineering.

So what criteria would I need to have met in order to treat a patient with this biosimilar? And I've broken it down into a few critical questions. The first is does the originator molecule have meaningful clinical value? Does the biosimilar have equivalent properties to the originator? Does the biosimilar have efficacy and toxicity profiles that are consistent with those of the originator?

Is extrapolation reasonable if biosimilarity has been demonstrated and will use of the biosimilar lower costs?

So let's consider each of these in turn. So firstly, does the originator molecule, filgrastim, have meaningful, clinical value? Clearly, the answer to that is yes. G-CSF has been used widely around the world for over two decades. The indications have already been described by

Dr. McCamish, and I won't go into them in any more detail, but this is a molecule which has unquestioned clinical value that clearly helps patients.

Despite that, I would submit that G-CSF is both underused and badly used. Here's a study from Choi and colleagues utilizing a retrospective analysis of U.S. Medicare databases to link many courses of chemotherapy for five different cancers to G-CSF use in patients who were receiving high risk chemotherapy. And as you can see on this slide, G-CSF was given to less than 50 percent of people who would have been deemed eligible receiving a high-risk chemotherapy regimen, and this was associated with a significant risk of chemotherapy and these neutropenic complications that required hospitalization.

In another studied by Kreys, et al, published last year in the Journal of Oncology Practice, it was shown that improved use of G-CSF can reduce emergency room admission rates significantly from about one-quarter, down to about

10 percent with associated savings related to the cost of care necessitated by emergency room admissions and subsequent hospitalizations.

In a really interesting study by Weycker, et al published last year, they took a look using a retrospective cohort design with all the caveats associated with that, looked at U.S. healthcare claims from 2001 to 2010 encompassing over 135,000 patients and many of whom had received daily filgrastim. This included all people who had received at least a single course of myelosuppressive chemotherapy and had received filgrastim.

As you can see from the small table on the bottom here, the use of filgrastim, according to guidelines, which would have been greater than or equal to 7 days, was associated with zero percentage mortality and relatively modest expenditures compared with those individuals who received significantly less filgrastim use. Most importantly here, the mortality rate increased as filgrastim use was diminished.

So does this biosimilar have equivalent properties as the originator? And again, just echoing what's been said by both speakers thus far, this is not a bioidentical, it's a biosimilar. Identical properties are not necessary -- in analytical components that were already described demonstrate that the structure, function, and bioactivity are either identical or highly similar to the originator G-CSF molecule. And at most, there are minor differences in formulation, so that the preponderant evidence in terms of the analysis of the properties supports biosimilarity.

Do Neupogen and Zarxio have similar efficacy and toxicities profiles? Again, echoing what was stated before, it's quite evident that the clinical program here is designed to be confirmatory of the analysis of biosimilarity because these analytical approaches are actually more sensitive than our clinical evaluations to evaluate this concept of biosimilarity. And the analysis of the clinical trial results just presented by Dr. Balser clearly support the similarity of the originator and biosimilar efficacy and toxicity profiles.

There is a vast worldwide experience with Zarxio, and I think this is really important for me as a physician and oncologist who sees patients. More than 7.5 million treatment days have been analyzed since 2009 across many different indications.

Now, the data that have been collected through pharmacovigilance and postmarketing analyses are not rigorously collected, randomized, controlled, perspective clinical trials, but this is a very large body of relevant information of interest. There have been no signs of unexpected toxicities or inefficacy. So from my perspective, this provides a comforting context for a prescribing physician.

In fact, the introduction of filgrastim biosimilars has coincided with an increase in G-CSF use in Europe. If you look at this chart here, you'll see that since 2009, there's been a roughly 30 percent increase in utilization of G-CSF, primarily due to the introduction of Zarxio, which, as you already heard, is now the dominant form of G-CSF being prescribed in Europe. And this has been associated with both improved utilization according to the guidelines, presumably because it's more readily available and lower cost.

So is extrapolation reasonable if biosimilarity is demonstrated? And for me, this is really where the rubber meets the road. Those of us who have been engaged in clinical trials of novel anti-cancer agents are accustomed to conducting clinical trials for different indications if there's a molecule that looks like it has significant antitumor activity or significant biological properties.

However, in the biosimilar concept, if the molecule is biosimilar and if it meets all the criteria for biosimilarity, then it stands to reason that extrapolation to the originator's indications is warranted, and I believe that's the case here. And again, the additional safety and efficacy context that's provided by the Zarxio worldwide experience certainly adds confidence that this is the appropriate direction to take.

So will the use of biosimilar lower costs? Well, I believe it's pretty clear that by increasing the availability of reagents through the biosimilar approach that competition will occur; that this competition will likely reduce costs, and the data from Europe support that.

There has been an increased utilization of guidelines since the institution of Zarxio, there have been improved clinical outcomes where this has been examined, and there's been a reduction of drug costs.

So what criteria do you need to be met for me to treat a patient with this biosimilar? In my brief presentation, I've shown you the various check boxes that I thought needed to be checked. In my judgment, they all have been checked, and I would feel very comfortable prescribing Zarxio to a patient or recommending that it be available to physicians.

Thank you very much. I'm going to turn the podium over to Dr. McCamish.

Applicant Presentation - Mark McCamish

DR. McCAMISH: Thank you, Dr. Weiner.

So I'll be discussing the totality of data just in four summary slides, and we're using the term "totality of the data." And that may be perceived as an overused term, but in this situation, it is critical to the foundation of biosimilarity because we're combining multiple evaluations of the molecule to look at the similarity, at the sameness of this molecule to the reference product. And I believe that we've gone through high level information that was submitted to the agency in the analytical and clinical.

This slide just summarizes the analytical, where Zarxio is highly similar to Neupogen. It has an identical primary structure as has been illustrated; highly similar secondary and tertiary structures just essentially overlapping; highly similar purity and stability profiles for the drug product; and then highly similar receptor binding and biological activities; so a lot of information for the base of this comparability, for the base of this biosimilarity assessment, prior to going into the clinical evaluation.

Then a summary of the clinical evidence, we've shown efficacy data that confirmed this similarity. We're fortunate with this particular biosimilar that there is a very nice PD marker, marker sets, so that PK and PD can be thoroughly evaluated, and that the absolute neutrophil count as well as the CD34 positive cell data really do confirm similarity to Neupogen in single-dose, multiple-dose, sub-Q, IV use, in a broad range of doses.

In the clinical trial, the duration of severe neutropenia was in the range of what was reported for Neupogen in this setting, actually a little bit lower in this clinical trial, and comparable between the two products; tight confidence intervals with lower boundary of approximately a quarter of a day in this trial; and the data as evaluated would also support equivalence determination within very tight limits.

As Dr. Weiner mentioned, extrapolation is justified by this totality of data, showing that the molecule is highly similar or essentially the same as the reference product and can be used in each indication that's there.

The summary of the safety data was also reviewed, showing that the incidence and nature of adverse events were similar for Zarxio and Neupogen. This is in the 302 study, as well as in the healthy volunteer studies; that there's really no concerning or unexpected safety findings throughout our entire program.

Even with repeated switching, we did not see a negative impact on immunogenicity or tolerance. And again, this was conducted for a future anticipation of considering interchangeability, which is not part of this initial file. But I think the data of this switching, showing no immunogenicity with switching, is important and supportive.

Then in the incidence and nature of AEs, they're similar throughout the postmarketing experience. And in this situation, it is unique in that this biosimilar has a lot of postmarketing information from other countries, which will not be the typical for biosimilar applications in the future.

So in summary, biologic drugs are important therapeutic agents. They are very costly, and there is an access issue that we're trying to address here. Modern technology and analytics allow for the full characterization and creation of biosimilars.

Zarxio's been demonstrated both analytically and clinically to be highly similar to the reference product, Neupogen, and this high similarity really does justify extrapolation to all indications for the reference product. And approval of Zarxio will expand options for patients and healthcare providers.

With that, Dr. Armstrong, I conclude the presentation by the sponsor this morning. Thank you for your time.

DR. ARMSTRONG: Thank you very much.

We are a little bit ahead of schedule, but I think this is still a good time to take our break. We'll now take a 15-minute break. It's 10:34, so we'll return at 10:50 exactly.

Panel members, please remember there should be no discussion of the meeting topic during the break, amongst yourselves or with any members of the audience. Thank you.

(Whereupon, a recess was taken.)

Clarifying Questions to the Presenters

DR. ARMSTRONG: I think we'll go ahead and get started. So we'll now take clarifying questions for the sponsor. For the panel members, please remember to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Thank you. Dr. Fojo?

DR. FOJO: Tito Fojo. So I had a question, a couple of questions, with regards to this. I think it's slide -- or figure 21 in the presentation -- not in your presentation, but in the document -- or figure 22, but actually as I'm looking at it -- yes, no, figure 22 in what we had to review. It's the one that shows the arithmetic mean serum concentrations of Zarxio and Neupogen.

I wonder if we could look at that and I had a question about that.

DR. McCAMISH: Slide up, please.

DR. FOJO: Yes. So actually this is a great experiment. I thought this was fabulous that you were able to take the Zarxio, put it in the acetate buffer, then Neupogen is in, and it's identical. And then you put it in the glutamate buffer, and it's not identical.

I think we can agree that this is, in fact, a real difference, that when you look at the concentration, there is less of it when it's been stored in the glutamate buffer than in the acetate or the Neupogen.

This is in kind of -- and this isn't meant in any negative sort of way. It's kind of swept under the rug because, well, the outcomes are similar, if you will, you know in terms of white count and so forth and so on.

But I wondered about this because there's mention about the fact that the Neupogen that was used was older than the Zarxio. I believe 30 months and 18 months were sort of like an average or no greater than -- because one was being bought, if you will, out in the market, and the other one was being produced by you. And I just wondered whether or not there might be some differences in stability between the two formulations.

So that would be my first question. Number 1, is this a real difference, and have you any thoughts as to why this is? And then if not, I wanted to follow-up with a couple of other questions.

DR. McCAMISH: Thank you. So let me try to address that. And we agree with you, this is a wonderful experiment in terms of showing the result and the perceptible difference in PK that one notices with the glutamate buffer. And to your point regarding stability, what we do is we evaluate and purchase Neupogen from the market. And it depends on the lots there, the time, et cetera. So we're never able to get it at O time, so it's always a little bit older.

This particular slide looks at stability over time. And you can see, again, red dots refer to Neupogen, blue refer to Zarxio. And you can see that we date it as negative 36 months because it's a three-year stability program, and we do not have data regarding the first 12 months for Neupogen.

You can see from a stability perspective, when you look at degradation as an example, that the degradation is the same in terms of rate constants. Ours starts a little bit lower in terms of degradation, but that's because we can provide our product newer to the market.

So when we've evaluated this, we've always evaluated the drug based on when we can purchase it from the market, and there's no evidence that stability over time is different, nor that we're out of stability and there's anything different with the drug substance when utilized.

In this situation, as you know, we did formulate this product, Neupogen, in our buffer, and we formulated ours in their buffer to show this. And there was no indication that the drug substance, the API, had any impact on the PK.

DR. FOJO: So you had this -- that in fact, the stability would appear to be the same. But then at the end, you were using a fresher product than you were with Neupogen. Right?

DR. McCAMISH: In this particular situation --

DR. FOJO: I mean overall.

DR. McCAMISH: Overall, there is a difference between these by about 12 months because ours is obviously 12 months newer. But it depends on where we purchase this. So sometimes it's the same from a timeline, and others different, but always within the stability criteria of the originator as well as our product.

DR. FOJO: And then if I could ask two simple questions. The CD, the circular dichroism, was that done in the storage buffer for each one, or were they diluted into comparable buffers?

DR. McCAMISH: So in CD when we're looking at this, we look at it both from the standpoint of API. So in that situation, it's in the API buffer. We also look at it from a drug product perspective, and then it's in its relative drug product.

DR. FOJO: So then we really don't know that they're identical in storage conditions.

DR. McCAMISH: In storage conditions, when you look at this over time, because we continue to --

DR. FOJO: The CD spectra that you showed that was superimposable, that is not reflecting what's really happening to the protein under storage conditions, right?

DR. McCAMISH: Let me ask from a perspective of -- on the analytic side, if Hansjoerg Toll can address that.

DR. TOLL: So the proteins were analyzed in the same buffer. And there is additional higher order structure method, which is not influenced by the buffer. It's HDX. So hydrogen deuterium exchange mass spectrometry, there we can compare the products in their respective buffer, and there you obtain the same result. Both products are highly similar with regard to the higher order structure in that case.

DR. FOJO: Okay. And then the last thing, why did you -- I see that you chose glutamate instead of acetate, it says in a couple of places for some patent reasons. But why did you chose a different pH?

DR. McCAMISH: That's the pH of the buffer itself. It wasn't a choice. That's there.

DR. FOJO: The pH is arbitrary.

DR. McCAMISH: Yes.

DR. FOJO: So why did you choose a .4 difference? Why not have it in the same pH conditions that the Neupogen is stored in?

DR. McCAMISH: That's a good question from a backup perspective. Hansjoerg Toll? You can use the other mic as well.

DR. TOLL: Just to clarify. If I understood the question correctly, you're asking me why we have used a different buffer for the development of the product compared to Neupogen.

DR. FOJO: I realize you had to choose glutamate over acetate for some patent issues, but then you pH'd it differently, 4.4 in your case, whereas Neupogen is stored at 4.0.

DR. SONDEREGGER: Corinna Sonderegger, pharmaceutical development at Sandoz, biopharmaceuticals. We had to select a different buffer and a different pH both due to patent reasons. That's why we have selected glutamate and pH --

DR. FOJO: Okay. I don't see why it couldn't have been similar pH, but that's okay.

DR. WALDMAN: So this is a follow-on question. What's your hypothesis about why the PK was different in different buffers? I know the difference is small, but why do you think they were different?

DR. McCAMISH: When you look at this from a perspective of bioavailability as well, you may have seen in the briefing book bioavailability is very close, 61, 59 percent. That's there. It's at subcutaneous injection, mobilization, others regarding pH adjustments, buffers. Don't know. I mean, in reality, we don't know.

Minor difference is perceptible. We've explained it. Doesn't have a relevant impact on the PD, which is an important marker, but really important question, and it's worth evaluating. But again, we're not able to say this is the exact reason.

Dr. Armstrong, if you would like, there were two prior questions by Dr. Roth and Dr. Willard [sic] that I could comment on if that would be appropriate.

DR. ARMSTRONG: Okay. Thank you.

DR. McCAMISH: So Dr. Roth, you were asking about the interchangeability issue in the community, how that might be perceived, and then Dr. Willard was asking about the do not -- dispense as written.

First, I want to remind you that this is applied for as a non-interchangeable biologic; biosimilar, not an interchangeable. So there are two distinct pathways here. And so, at this point in time, for the first approval it's a non-interchangeable.

But to get to your question, in the community from an interchangeable perspective, if you had a interchangeable biologic that was there, and the physician wrote for let's say Neupogen in this case, and if it's non-interchangeable, as this product will be, even if there's a formulary issue driving it, the pharmacist will still have to contact the physician if they make a change for a non-interchangeable product.

So let's say you write for Neupogen and the formulary says Zarxio is higher on the formulary, the pharmacist cannot make that switch. They have to contact a physician to make that switch. So it's similar to formulary uses now.

Now this is driven, as Dr. Christl mentioned, on a state level. And what I can say is from a state level, all of the legislation that has passed and has been considered allows for the physician to make that determination and to have dispense as written. So there's really no difference here that would be experienced on a community basis than what we've seen before. But again, this application is for a non-interchangeable designation biosimilar.

DR. ARMSTRONG: Dr. Mager?

DR. MAGER: Don Mager. I just wanted to follow up on the analytical assessment, and I was wondering if the kinetics of the change in higher order structure was evaluated under stress conditions such as thermal or mechanical stress.

DR. McCAMISH: We evaluated mechanical stress as part of the stability component, which includes higher order evaluations. So we included stability, shipping, stress, temperature, et cetera, and looked at the higher order structure with all of those, and higher order structure was not impacted by those over time.

DR. ARMSTRONG: Does that answer your question?

DR. MAGER: Thank you.

DR. ARMSTRONG: Dr. Liebmann?

DR. LIEBMANN: So in previous meetings of this committee that I've been to, I think that cost has been sort of the elephant in the room that nobody acknowledges. And I was actually pleased to see that your consultant acknowledged it prominently and said that he expects that if this is approved, this will lead to significantly lower costs. I then noticed that in the final summation from the company, there was no mention made about that.

So my question is, is the consultant correct? Would this really bring down costs?

(Laughter.)

DR. McCAMISH: Okay. I like elephants in the room, so let's talk about that. That's our passion is to have an impact on use, and we do that through cost. So let me give you a little bit of information about our European experience, and then I'd like to ask Dr. Blackwell to come up and comment on the clinical side as well, based on her experience and how she would use this in anticipation and to access.

So in Europe itself, in the introduction of the biosimilars in 2009, there has been a substantial increase in the use, so we are addressing access. It has been a substantial reduction in cost because of the competition that's there.

DR. LIEBMANN: May I just suggest that pricing in the United States in healthcare is markedly different than pricing in Europe, and so I'm not sure that that's a relevant model to point to.

DR. McCAMISH: No, I agree with you that the models are, in fact, different in price. What I was mentioning is cost. So you're absolutely right. Price will be very complicated, and it could be that our price would be at parity, but the cost would be lower. And there's all sorts of things that come into that, whether it's rebates and other types of situations. But what I can give you is the experience we've had.

In Europe, there are many different systems, some of which may be more applicable than others, and that it has had a huge impact on the use, as well as on price. And most people acknowledge a 20 to 30 percent price reduction that's theirs, but it depends on the state and the area.

Dr. Blackwell, if you would like to come up and comment on this and your patients.

DR. BLACKWELL: Sure. I'm Dr. Kimberly Blackwell, a medical oncologist, and I do have a conflict in that I'm being compensated for being here today, as well as my participation in the DSMB.

As an American medical oncologist, I've not had an opportunity to prescribe Zarxio to my patients. Dr. Harbeck and other of the consultants have actually prescribed the drug. But I think it is an elephant in the room, not just in terms of cost but access to some of these very costly supportive care medicines. And as someone who sees patients three full days a week, it's not just the total cost of the drug that affects access. It's the co-pays associated with it. It's the formulary decisions.

Even in this week, I've had patients

receiving adjuvant TAC chemotherapy who have chosen to actually take off work to come and get their G-CSF so that they don't have to pay the $20 to $40 co-pay associated with the cost of some of these medicines. It's not even the total cost. It's the cost to the patient. It's the cost to society.

So although I can't predict what the pricing would be, the sponsor would have to address that, I believe that options will improve access and hopefully make a significant contribution to the cost to the patient, whatever that might be. Thank you.

DR. LIEBMANN: I'll just say that the point of my question was I was hoping that the sponsor would address it.

(Laughter.)

DR. McCAMISH: Thank you.

DR. LIEBMANN: You know, let's be honest. In fact, it's not complicated. There is a price of Neupogen. You could simply say that as a new entry into the market -- and I don't expect you to. And trust me, I'm not going to base my vote on the cost because that's not an issue that comes up in our vote here. But you could simply say, yes, we're going to price it less than Neupogen. All right. And if you're honest, that would be delightful.

(Laughter.)

DR. McCAMISH: I understand. Let me say that we can't say that the price will be less because in some situations, the price will be at parity because of other relative terms that will come into existence that's there. The cost will be less to the consumer, to the payer, to the healthcare economy. It has to be. Otherwise, it doesn't make sense. But price is a relatively complex situation. I can give you examples.

Now, this is the first biosimilar file to come to the States. We have had experience with a biosimilar drug that we took through a 505(b)(2) approach in the States, because the 351(k) wasn't available, and that's another protein growth hormone.

We were the seventh to the market with growth hormone. And when we came to the market, this was quite a ways back, there was a learning on our part because of the complexities that you've actually mentioned. And we priced this quite low from the beginning, and that reduction was substantial; almost half.

With that, we had difficulty selling the drug at all because the incentive for a specialty pharmacy was that they get a percentage of the price of the drug, and that was about a 6 percent incentive. So by pricing it that low, they had a huge disincentive not to use the drug.

Now, for managed care organizations, that disincentive doesn't exist because they're looking at the total overall price. And with that, we had very good penetration, very good use. But that was a huge learning to us that price is not as easy as one would expect, and we can't just say the price is going to be X because various components work differently.

But the reality is, we moved from number 7 in the marketplace to competing with number 2 or 3 because the cost of using our product is lower.

DR. STRONCEK: Dave Stroncek. I have a question about a slide, stem cell mobilization study 105. And it's the slide on page 32 of the handouts by the company, the non-interventional study in healthy unrelated stem cell donors.

One of the study's objectives was long-term safety assessment, yet, no data was shown. Can you comment on what parameters you're looking at for long-term safety effectiveness and do you have any data back yet?

DR. McCAMISH: Thank you for the question, and you know better than all of us in terms of the risk to healthy volunteers. You've published on this, and you've expressed your concern, which we agree with. So in this situation, you're taking healthy individuals. They're donating, and you want to find out what those long-term effects are, so we're looking at immunogenicity.

But in reality, the major question here that has been asked is whether there is a long-term impact on myelodysplasia and other tumor types of things. So this is a 10-year follow-up, and obviously we don't have the 10-year data, but the data thus far show no signal again of any concern that's there. But this is part of a long-term commitment that most G-CSF companies are involved with to look at this issue.

DR. ARMSTRONG: Did that answer your question?

DR. STRONCEK: Yes.

DR. ARMSTRONG: Okay. Dr. Roth?

DR. ROTH: Bruce Roth. I had a question for Dr. Balser. My gestalt, and perhaps incorrect from this morning, is that we have a little bit less robust information about induction of CD34 positivity than the other parameters that we've talked about today, and yet that's the most important parameter for the one indication of mobilization. I say less robust in that the 109 data is not powered for equivalency, and I think, as you've said, the 501 study is still ongoing.

So it would seem that if that's the case, it's a little bit bigger leap of faith to extrapolate from the rest of these parameters and indications to the indication of mobilization.

DR. BALSER: Well, thank you for your question, and I understand your concern. In the 109 study that I presented, which was the single-dose study, we had the CD34 positives at the secondary parameter. But I also showed the results from the multiple-dose studies that we had conducted, where again we had a crossover design and we had seven applications in each of the two periods.

You saw that the dose response was very similar between the two products from a 2.55 up to a 10 microgram per kilogram dosing, which we think this really establishes overall -- this is what I had shown previously. If you look at the lower right display of the CD34 positives, that response, you see that this is absolutely identical for all the three doses that we have studied in the multiple-dose setting. And I believe that this really provides confirmation of the similarity in the response, also in this particular setting.

DR. ARMSTRONG: I had two questions, one of which I will probably hold, but when you talked about the crossover study, we didn't see a lot of data past cycle 1, and I'm sort of interested in if you saw anything of interest in the crossovers, the 302 study and the crossover with that in terms of any of the parameters that you were looking at past cycle 1.

DR. McCAMISH: Go ahead.

DR. BALSER: Yes, I agree. This probably is an interesting piece of the study as well, even though we don't pursue interchangeability of that point. But also if you look at the switching part of the study, there was nothing, which was unexpected.

In particular, if you look, for example, at the immunogenicity, which we have shown, even in the switching arms, there were no signs of immunogenicity. And if we look at the adverse event profiles, although they are the same essentially in all four groups, being them either continuously treated or being exposed to repeated switching. And the same holds true if you look at the efficacy parameters.

DR. ARMSTRONG: Thank you. Dr. Fojo?

DR. FOJO: This is as much addressed to the company as to the FDA. So in slides 43 and 44, for example, it's talked about equivalence, but is that really equivalence? Is that what the FDA's sees this as? And then also, in the primary objective of EP06302 was to assess similar efficacy. Is that what the FDA thinks all of this was, equivalence and similar efficacy, or were these more of a non-inferiority design, the way they were targeted??

DR. McCAMISH: If you want -- do you want us to respond to that or --

DR. FOJO: I guess I wanted the FDA to respond.

DR. McCAMISH: Okay.

DR. CHRISTL: I think it would be best to raise the question again once FDA goes through their presentation of the data, so that you can hear from them, their presentation, and see if you have any questions after that. Certainly, if

Sandoz wants to weigh into that, that's fine as well.

DR. McCAMISH: Could we bring up the backup slide of regulatory interactions? I think it's important to realize that the development of this product as a biosimilar spans a six-year interaction with the agency, and this interaction started in October of 2009, prior to the passage of BPCIA, when both the agency and we as a sponsor, were learning the paradigm shift necessary for production of a biosimilar.

DR. FOJO: Okay. Just in the interest of time, this is not going to answer what I was asking. I was just asking a question about a word, "equivalence," and you'll probably spend five minutes doing this, and we'll waste time. So I guess I'll wait for the FDA to --because related to that, in terms of -- I mean, the FDA had this in their thing. They said 1 day of DSN difference is not clinically meaningful. That had no reference to it.

This seemed to have been a number that was pulled out of the hat, and I suspect that it was. In the company's analysis of this, they talk about how the DSN for chemotherapy with Neulasta was 1.4 days, as opposed to, I think it was 6 days with nothing.

So this then morphs into that's the DSN for Neupogen and for this compound. And not really. That's the DSN for Neulasta, which is a different compound all together. And then out of that comes the 1 day, which is, okay, 1 day out of 5.6 is less than 20 percent, will be above that 80 percent.

It's just a little smoke and mirrors as to how we get to this, and there's no clarity about that. And I think since this is the test case, we should probably make sure that those things are clear going forward. And the company then goes on and says, well, one day -- and then it seems that, well, one day, well because everybody else uses 1 day.

I suspect that 1 day was never properly established, and I suspect if we had a thousand patients in one arm and a thousand in the other, and a thousand had one more day of DSN than did the other arm than the control arm, let's say, there would probably be a clinical difference that would probably be managed with antibiotics and so forth and would probably in the long run not make a lot of difference in terms of let's say survival, but all of these numbers are just being pulled out without really sound basis for it.

DR. ARMSTRONG: Well we have a chance to go through this in more detail at the agency presentation. Thanks.

DR. FOJO: Okay, fine.

DR. ARMSTRONG: Dr. Laport?

DR. LAPORT: This is Ginna Laport, a question for Dr. Balser going to study 501. You said this is a long-term follow-up of the unrelated stem cell donors. It says the data cutoff was over a year ago. What's the median follow-up so far to say that there's been no long-term effects observed?

DR. McCAMISH: Dr. Balser do you have -- don't know. Okay. We don't know the median follow-up right now. The data cutoff was for this filing.

DR. LAPORT: My second question then to Dr. Balser, I'm just curious. This is a study on unrelated donors. Was there a reason that there was not a study or is there ongoing study on related stem cell donors?

DR. BALSER: No, actually we do have studies as well in the other setting. I was just pointing to this one as an example of the data that we have generated in the indication.

DR. ARMSTRONG: Dr. Bensinger, you're next.

DR. BENSINGER: Bill Bensinger. I know this isn't in your submission package, but do you have any comparative data on engraftment kinetics of these mobilized stem cells?

DR. McCAMISH: We do not have comparative engraftment data.

DR. ARMSTRONG: Dr. Moreira?

DR. MOREIRA: Thank you. My question relates to slide 34 in today's presentation, where the data on content for commercial and clinical batches was presented. I was wondering if there is any difference in manufacturing between those types of products, and if there are any differences, what are they?

DR. McCAMISH: Thank you for the question. Could we have the backup slide on manufacturing as well? There are no differences in the manufacturing for this, between the clinical and the commercial. It was at commercial scale, same facility, both for drug product, as well as for drug substance. And if you look at the information that we addressed, you can see here the clinical, commercial, and the combination.

As you see in the middle sector here, you see the comparison between Zarxio commercial, clinical, and Neupogen U.S. showing no relative differences. Remember that the release specs for these products are between 95 and 105 percent from a content perspective. And what happened is that when we submitted the initial manufacturing batches, they happened to be low-ish on that, but still well within release specs. So FDA wanted us to submit additional manufacturing batches, which we did, and that allowed us to have a better representation.

You can also see that and if you compare the green in the middle section with the pink on the right-hand side, and you can see by eye, that the Neupogen U.S. looks perhaps to be lower than Neupogen EU. But again, this is simply related to the number of batches that were looked at, as you have a little bit more variability that's there. But the manufacturing did not change in this situation.

DR. ARMSTRONG: Did that answer your question?

DR. MOREIRA: Yes.

DR. ARMSTRONG: Thank you. All right, I think -- yes, one more question.

DR. NEVILLE: Sorry. The question is, what is the experience with pediatrics and young adults in Europe, and what are your plans here? Because we've talked about extensive use in Europe, but I haven't heard anything about kids or young adults.

DR. McCAMISH: So for that, I'd like to call Dr. Paul Cornes who has experience directly in this situation.

DR. CORNES: Thank you very much. I'm Dr. Paul Cornes from the Bristol Hematology and Oncology Center. I've got some disclosures. I've received funding from Amgen as a consultant and a speaker, as well as funding today for appearing for Sandoz.

The pediatric data we've got, my hospital, like a lot in the U.K., we switched within a year 90 percent of G-CSF in the United Kingdom, went from originator to biosimilar, and we have one stock at our hospital, and it's used for children in my work in the pediatric as well as the adult clinics.

Our data on patients that are that are our young patients is entirely physician driven, and you'll see its small numbers. But it's in the context of 7.5 million doses of this drug in Europe, which we think equates to around 300,000 patients treated over the last six years. For unusual events, we know that the European pharmacy vigilance database, EudraVigilance, is very good.

When a biologic drug has a biosimilar equivalent, we think that we're more than 95 percent likely if there's an adverse event to track it back to the exact brand and batch. And when we've used that to look at the safety of this drug, because we're worried about rare events in these vulnerable groups, we've tracked back -- the things we're worried about would be immunogenicity; so things that you couldn't predict from the class of the drug.

There are only three cases of immunogenicity causing anti-drug antibodies in the world's database, and they're based on three patients from the USA where this drug isn't sold, and it's patients that had filgrastim concomitantly with another drug, and it was those drugs that had the anti-drug antibodies.

So I didn't see from the class of this drug -- there are class-related problems, expanding white cell counts in young people, but I didn't see that there's an immunogenetic problem, based on the totality of the data that we have on the enormous number of patients treated in Europe.

Does that help you?

DR. NEVILLE: Yes.

DR. CORNES: Thank you.

DR. ARMSTRONG: Thank you. So we're going to move on now to proceed with the presentation from FDA.

FDA Presentation - Albert Deisseroth

DR. DEISSEROTH: My name is Albert Deisseroth. I'm a medical officer team leader in the FDA. My role will be to provide you with an introduction to the FDA presentation. On May 8th, 2014, Sandoz submitted BLA 125553 requesting licensure of EP2006 as a biosimilar to U.S.-licensed Neupogen.

The interchangeability designation, as has been mentioned before, was not requested by Sandoz. Sandoz requested licensure of EP2006 as a biosimilar to U.S.-licensed Neupogen for all of the five indications for which U.S. licensed Neupogen is licensed. These indications include cancer patients receiving myelosuppressive chemotherapy to decrease the incidence of infections as manifested by febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever. This indication was approved in February 1991.

Bone marrow transplant, to reduce the duration of neutropenia and neutropenia-related clinical sequelae, febrile neutropenia in patients with non-myeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation. This indication was approved June 15th, 1994.

Severe chronic neutropenia for chronic administrations to reduce the incidence and duration of sequelae in neutropenia, fever, infections, oropharyngeal ulcers in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. This indication was approved December 1994.

Mobilization of peripheral blood stem cells for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis. This was approved in December of 1995 in patients with AML receiving chemotherapy for reducing the time to neutrophil recovery and the duration of fever following induction and consolidation chemotherapy treatment of adults with AML. This was approved in 1998.

This slide is an overview of the development of EP2006 outside of the USA. By the way, I'm using the designation EP2006 instead of Zarxio, because Zarxio has not been approved as a proprietary designation for this drug.

On February 6th, 2009, Sandoz's EP2006 was approved for marketing in the European Union under the name Zarxio as a biosimilar product to EU-approved Neupogen. As has been alluded to by previous speakers, marketing experience with Zarxio outside the U.S. includes in excess of 7.5 million days of patient exposure.

This slide summarizes the approach that the

FDA uses to assess the demonstration of biosimilarity. FDA intends to consider the totality of the evidence provided by a sponsor and recommends a stepwise approach to demonstrating biosimilarity, which can include a comparison of the proposed biosimilar product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics and pharmacodynamics, clinical immunogenicity, and clinical safety and effectiveness.

This slide summarizes Sandoz's approach to demonstrate biosimilarity of EP2006 to U.S.-licensed Neupogen. Sandoz provided extensive analytical characterization of the proposed biosimilar and U.S. licensed Neupogen.

Sandoz provided data and justification for a scientific bridge between EP2006, U.S.-licensed Neupogen and EU-approved Neupogen. Sandoz provided nonclinical toxicity and PK/PD data comparing EP2006 and EU-approved Neupogen.

Sandoz provided PK/PD studies in normal human subjects comparing EP2006, U.S.-licensed

Neupogen, and EU-approved Neupogen. Sandoz provided immunogenicity studies comparing EP2006, and U.S.-licensed Neupogen and EU-approved Neupogen.

Finally, Sandoz provided clinical safety and efficacy effectiveness data comparing EP2006 and U.S.-licensed Neupogen.

This slide summarizes the order and content of the FDA presentation. First, Drs. Gutierrez-Lugo and Dong will provide the summary of the review of CMC studies that involve comparative analytical similarity and a scientific bridge for EP2006, U.S.-licensed Neupogen and the EU Neupogen.

Then Dr. Chris Sheth will provide the results of the review of the comparative toxicity and PK/PD studies in rodents for EP2006 and EU Neupogen.

Third, Dr. Sarah Schrieber will review the analysis of single and multiple-dose PK/PD studies in human subjects.

Fourth, Dr. Susan Kirshner will provide a review of the studies relating to comparative antidrug antibody responses to EP2006, U.S. Neupogen, and EU Neupogen.

Fifth, Dr. Donna Przepiorka will summarize the FDA review of clinical studies in patients with breast cancer. Then I will return to the podium to summarize FDA's recommended action based on the totality of evidence provided by Sandoz.

Now I call to the podium Dr. Gutierrez-Lugo to initiate the review of the CMC data.

FDA Presentation - Maria-Teresa Gutierrez-Lugo

DR. GUTIERREZ-LUGO: Good morning. My name is Maria-Teresa Gutierrez-Lugo. I am a chemistry reviewer in the Office of Biotechnology Products, and I will present the summary of the review of the chemistry, manufacturing, and control section of Sandoz 351(k) BLA to support the proposed biosimilar product EP2006.

Before I continue, can everybody hear me in the back? Okay, good. Thank you.

In this presentation, I will provide a general background on the structure and mechanism of action of granulocyte colony stimulating factor or G-CSF, followed by brief information on EP2006 manufacturing, and the studies provided by Sandoz to support biosimilarity. And then I will present the agency review of the analytical similarity data.

It was alluded earlier that G-CSF is a relatively small protein of 175 amino acids with a molecular mass of approximately 18.8 kilodaltons. A representation of the primary structure of G-CSF as reported in the literature is shown on the left side of your screen.

G-CSF is produced naturally by humans and other species, and also produced recombinantly in the host cell, E. coli. Recombinant G-CSF is non-glycosylated. Due to the lack of complex post-translational modifications, G-CSF can be purified to almost homogeneity and be subjected to extensive analytical characterization.

In the scientific literature, there is relevant knowledge on the structure and function relationship of G-CSF, including the impact of chemical modifications on the biological activity of G-CSF. For example, it has been reported that oxidation of methionine residues reduces potency.

Reports in the literature also describe that the G-CSF receptor plays a critical role on the biological activity of G-CSF related to the general indications of neutropenia and mobilization of hematopoietic stem cells. In the figure on your right, there is a representation of the complex of G-CSF and the G-CSF receptor and the binding epitopes of G-CSF in black circles, determined by structural studies.

Chemically small faction [ph] related to the general indications of neutropenia involves binding of G-CSF to the G-CSF receptor on blood cells of the neutrophilic granulocyte lineage. The binding initiates signal transduction, represented in the figure, that leads to the proliferation and differentiation of neutrophil committed progenitor cells into neutrophils. It also increases the mature neutrophils in the blood, which is an acceptable pharmacodynamics marker or PD marker.

My colleague from the Office of Clinical

Pharmacology is going to make reference to these PD markers as absolute neutrophil counts, or ANC, in her presentation. Finally, the signal transduction leads to the enhanced neutrophil function.

The details of the mechanism of action related to the mobilization of hematopoietic stem cells is not fully understood. However, there is strong evidence in the literature indicating that the G-CSF receptor plays a critical role in the mobilization of hematopoietic stem cells. This slide represents a model of G-CSF mediated mobilization reported in the literature.

On the left panel, there is a presentation of hematopoietic stem cells under baseline conditions. Hematopoietic stem cells are retained in the bone marrow through key interactions expressed on the surface, such as VLA-4 and c-kit with molecules expressed on the surface of osteoblasts lineage cells such as VCAM-1 and kitL.

Under G-CSF mediated mobilization, represented on the right panel, G-CSF binds to the G-CSF receptor in this model on monocyte lineage cells. The binding initiates the production or suppression of currently undefined transacting signals that leads to the suppression of osteoblasts lineage cells. The net effect is the disruption of key interactions that regulate hematopoietic cell function and leads to the mobilization of hematopoietic stem cells into the blood stream.

Hematopoietic stem cells are identified by the presence of the cluster differentiation marker 34 on the surface. This is also a relevant pharmacodynamics marker for hematopoietic stem cells mobilization. My colleague from the Office of the Clinical Pharmacology is going to make reference to this PD marker as CD34 cell counts.

I'm now going to present summary information about manufacturing of EP2006 drug substance and drug product. EP2006 drug substance is produced by recombinant technology in E. coli cells. The EP2006 drug substance process consists of various steps that purify G-CSF from other E. coli proteins.

Process-related impurities such as host-cell DNA and host-cell proteins and other process-related impurities specific to the EP2006 process were evaluated. Sandoz provided data to demonstrate that the EP2006 manufacturing process is able to reduce the levels of these impurities to very low levels; for example, to the levels of part per million for host cell proteins and picogram levels for host cell DNA. These low levels of process-related impurities are appropriate for biotechnology products.

The EP2006 drug product is manufactured in pre-filled syringes, and it has the same strengths approved for U.S.-licensed Neupogen. The strengths are 300 micrograms of G-CSF in .5 milliliters, and 480 micrograms of G-CSF in .8 milliliters. The formulation, as we heard earlier, of EP2006 differs from that of U.S. licensed Neupogen in one inactive ingredient.

As in many biotechnology development programs, the manufacturing process of EP2006 drug substance and drug product change during clinical development. Sandoz provided data to demonstrate that EP2006 proposed commercial drug product is comparable to the EP2006 drug product used in the clinical studies. Comparable in this context means that the product quality attributes of EP2006, before and after manufacturing changes made by Sandoz on their own product, are highly similar, and there is no expected adverse impact on the safety and efficacy, including immunogenicity.

In addition, Sandoz provided data to demonstrate that the EP2006 drug substance and drug product processes are validated and produce product consistent quality and demonstrate that the controls of EP2006 drug substance and drug product meet regulatory expectations. Lastly, the initial assessment of the facilities where EP2006 is manufactured indicate consistency with good manufacturing practices.

To support biosimilarity of EP2006 in the reference product, U.S.-licensed Neupogen, Sandoz provided data -- the results from five pharmacokinetic and pharmacodynamic similarity studies, five nonclinical studies, and two clinical studies.

All studies except EP06109 and EP06302 used a Neupogen product that had been approved by the European Union as active comparator. These non-U.S.-licensed comparator products may be referred throughout FDA presentations as EU-approved Neupogen or EU Neupogen.

As we hear in Dr. Christl's presentation, the use of the EU-approved Neupogen as active comparator in some of the clinical studies listed here requires a scientific bridge between the three products.

I am now going to provide a summary of Sandoz's approach to assess analytical similarity and the agency review of analytical similarity data. The data corresponds to Sandoz analyses of U.S.-licensed Neupogen, EU-approved Neupogen, and EP2006.

In their 351(k) BLA submission, Sandoz provided analytical data from up to 20 lots of EP2006 drug product, including the clinical and commercial drug product. The analytical studies included clinical drug product lots used in 4 of the clinical studies and 2 of the nonclinical studies listed in the previous slide.

In addition, 6 lots of drug substance, 10 to 15 lots of U.S.-licensed Neupogen, and 34 to 52 lots of EU-approved Neupogen were analyzed. The number of lots analyzed for each quality attribute were considered assay variability and availability of material.

The U.S.-licensed Neupogen and EU-approved Neupogen lots analyzed span approximately 5 and 10 years, respectively, and include lots across the shelf life of the products. The EP2006 lots analyzed were manufactured between June of 2004 and November 2005 -- these are for the clinical lots, and July and August of 2011 for the proposed commercial lots. Analytical testing was conducted before expiry of the two products.

Now, it is important to indicate that for this development program, various analytical comparisons need to be made. One is analytical comparison between EP2006 and U.S.-licensed Neupogen. This comparison is used to support a demonstration that EP2006 is highly similar to the reference product, U.S.-licensed Neupogen.

Pair-wise analytical comparisons between EP2006 U.S.-licensed Neupogen and EU-approved Neupogen -- are used to support the analytical bridge between the three products. The bridge is needed to justify the relevance of the data generated using EU-approved Neupogen as a comparator in some of the clinical and nonclinical studies intended to support demonstration of biosimilarity to U.S.-licensed Neupogen.

This table provides a list of the quality attributes evaluated and some of the orthogonal methods used to assess analytical similarity. The analytical methods evaluated physicochemical properties of the products such as primary structure and [indiscernible] of the structure, the functional properties of the product, including receptor binding and biological activity, and product-related substances and impurities among other quality attributes.

In addition, comparative stability studies using the stability indicating methods were also conducted. The methods used in the analytical studies were validated or qualified at the time of testing and demonstrated to be fit for intended use.

In the next slides, I will provide a summary of the analytical comparisons. Given the time constraints of this presentation, I selected three critical quality attributes for discussion to provide an example of the agency approach to review analytical similarity data.

The critical quality attributes that I selected are primary structure, bioactivity, and protein content. These critical quality attributes are considered of very high criticality based on Sandoz critical quality attribute assessment. Review of analytical similarity was based on data and information provided by Sandoz.

The primary structure of the three products was evaluated by N-terminal Edman sequencing, top-down mass spectrometry, and peptide mapping with UV and mass spectrometry detection. The N-terminal Edman sequencing results show that the three products have the same seven N-terminal amino acids.

The peptide map provides more detailed information about the primary structure of the products, including the location of two disulphide bonds in the molecule. The disulphide bonds are located between cysteine 37 and cysteine 43, and between cysteine 65 and cysteine 75. The peptide map method consists in cleaving the protein of interest in the smaller peptides using specific proteases. The resulting peptides are separated by chromatography methods and analyzed by mass spectrometry, which provides information about amino acid composition.

In this figure, there is a representation of cleaved peptides separated by reverse-phase HPLC detected using a UV detector. The first peptide from the bottom corresponds to EP2006 reference standard, followed by three peptide maps of commercial EP2006 drug product, which are compared to two lots of U.S.-licensed Neupogen. These are the next two lots, 1014928 and 1025269, and one lot of EU-approved Neupogen. That's the very top chromatogram.

From this figure, it is evident that the peptide maps of the three products is similar with respect to the number of peaks, retention time in peak areas. In addition, the mass spectrometry data, not shown here given the extensive amount of data, show that the peptide masses of each of the peptides represented in the maps are in agreement between the three products and in agreement with the theoretical masses based on the sequence of G-CSF reported in the literature, including the location of the disulphide bonds.

To further support correctness of the primary structure. The molecular mass of the three products was evaluated by two mass spectrometry techniques. The results indicate that the molecular mass between the three products is an excellent agreement. Actual differences in molecular mass between the products using electrospray mass spectrometry with high accuracy is less than one dalton or less than the molecular mass of one hydrogen.

The molecular mass of the three products is also consistent with the theoretical molecular mass of recombinant G-CSF reported in the literature. In addition, tandem mass spectrometry analysis or sequencing of EP2006 digested using three different proteases, and sequencing of the EP2006 expression construct indicate that the primary structure of EP2006 is identical to the sequence of G-CSF reported in the literature.

So based on the data summarized in these two slides, it was concluded that the primary sequence of EP2006 U.S.-licensed Neupogen and EU-approved Neupogen is the same.

The second critical quality attribute that I will discuss is biological activity. The biological activity of the three products was measured using an NSF-60 cell proliferation assay. The NSF-60 cell line is a murine myelogenous leukemia cell line that expresses the G-CSF receptor.

The figure on your right is a representation of the biological activity of the two products. The biological activity was measured relative to Sandoz reference standard, calibrated against an international G-CSF reference standard and is reported as percentage of bioactivity.

The biological activity of EP2006 drug product is represented in red symbols. The closed red symbols correspond to the EP2006 manufactured by the proposed commercial process, and the open red symbols is the biological activity of EP2006 manufactured by the clinical process.

The closed green triangles correspond to the biological activity of U.S.-licensed Neupogen pre-filled syringes, and in open triangles is the biological activity of U.S.-licensed Neupogen in vials. The last set of data is the biological activity of EU-approved Neupogen lots.

Descriptive statistical analysis and visual examination of the data, the graphical data, supported that the biological activity of two products is similar. And to further support analytical similarity, statistical analysis using equivalence testing was conducted by Sandoz. The agency also conducted the statistical analysis to confirm Sandoz's assessment. Both the statistical analyses included bioactivity results for U.S.-licensed Neupogen in pre-filled syringes and vials.

The figure shown in the slide is our presentation of the pairwise comparisons between the products under evaluation. The statistical analysis depicted in the figure was conducted by the agency and will be discussed in detail by Dr. Dong in the next presentation. Briefly, the biological activity of the three products is a statistical equivalent with respect of the mean values and support analytical similarity in the analytical bridge.

Similar approach used for the biological activity was applied for the protein content. The protein content data are expressed as percentage of declared content. In this figure, the red squares correspond to the percentage of the declared content of EP2006 manufactured by the commercial drug product, the red diamonds is EP2006 manufactured by the clinical process, and the green and purple symbols correspond to U.S.-licensed Neupogen and EU-approved Neupogen data.

Once more, the percentage of declared content of the two products was found to be statistically equivalent, and the results support that the two products have the same strength and also support the analytical similarity of EP2006 and the analytical bridge between the products. Once more, the statistical considerations to analyze the bioactivity data and the content data will be discussed by Dr. Dong.

These slides provide a summary of the review of the analytical comparisons between EP2006 U.S.-licensed Neupogen and EU-approved Neupogen. The agency review of the analytical similarity data indicate that the amino acid sequence of the two products is the same in that all quality attributes evaluated are highly similar. For product-related species, for example, oxidized species, highly similar means the same type of oxidized species and similar levels of each oxidized individual species in the products to be in similar levels.

In addition, the comparative stability data indicate that the three products have similar stability profiles, judged by similar degradation kinetics under accelerated conditions and same type of degradation products.

In conclusion, the pairwise analytical comparison of EP2006 U.S.-licensed Neupogen and EU-approved Neupogen support the scientific bridge based on the relatively simple structure of the protein, the lack of post-translational modifications, and the robustness of the pairwise analytical characterization. Therefore, the data derived from studies using EU-approved Neupogen as active comparator may be used to support the demonstration of biosimilarity of EP2006 and U.S.-licensed Neupogen.

Finally, the agency concludes that the

extent of analytical characterization of EP2006 and the comparator products is robust. The EP2006 clinical and commercial process is analytically highly similar to U.S.-licensed Neupogen. The analytical similarity data do not raise residual uncertainty about the similarity of EP2006 and U.S.-licensed Neupogen. The impact of the EP2006 formulation on pharmacokinetics and pharmacodynamics will be discussed in the nonclinical and clinical studies. Thank you for your attention.

FDA Presentation - Xiaoyu Dong

DR. DONG: Good morning. My name is Xiaoyu Cassie Dong. I'm a CMC statistical reviewer from Office of Biostatistics. In this presentation, I'm going to give you more details on statistical equivalence testing for bioactivity and content. And this part was also briefly mentioned by my colleague, Terry's presentation earlier.

My talk today will be in four parts. I will start with an introduction of the statistical equivalence testing followed by the testing results of bioactivity and content. At the end of my talk, I will make conclusions.

Just a recap from Dr. Christl's presentation earlier, this page gives you a summary of FDA advice on statistical analysis of analytical similarity data for EP2006. In this presentation, I will only concentrate on the tier 1 approach equivalence testing for some high-risk attributes. I also would like to clarify that the testing results and approach in this presentation are from agency's analysis, not from Sandoz analysis.

For EP2006 bioactivity and content are two critical quality attributes for tier 1. Their analytical similarity was tested by statistical equivalence testing in which the mean values from a test product and a comparator are considered to be equal if their main difference is entirely within an equivalence acceptance range from negative 1.5 times sigma C to 1.5 times sigma C. The sigma C here is the variability of the comparator, and I will give you more information on sigma C in the next slide.

In practice, the true mean difference is usually unknown, so we can use the confidence interval to test on the hypothesis of equivalence, that is to conclude statistical equivalence in mean values if 90 percent confidence interval of the mean difference is completely within the equivalence acceptance range.

As I mentioned here, in the equivalence range, the equivalence margin is defined as minus plus 1.5 times sigma C. Again, sigma C is the variability or the standard deviation of the comparator, which can be either U.S.-licensed Neupogen or EU-approved Neupogen, depending on the specific analysis being conducted. In addition, sigma C is estimated from Sandoz data on Neupogen products.

This specific margin is defined based on approach to assure sufficient power of passing equivalence testing with a given number of laws when the true mean values are close to each other.

That's an overview of statistical equivalence testing. Now, let's take a look at the testing results for content. Recall the bioactivity data points are reported as percentage of potency relative to Sandoz in-house reference standard.

In the data set, we have 15 EP2006 lots, 15 U.S.-licensed Neupogen lots, and 34 U.S. approved Neupogen lots. These graphs here summarize the statistical equivalence testing results for the three pairwise comparisons of EP2006 versus U.S. Neupogen, EP2006 versus EU Neupogen, and EU Neupogen versus U.S. Neupogen.

In each graph, the vertical line is the 90 percent confidence interval of the mean difference. The horizontal red bars are the equivalence margins. As you can see, all 90 percent confidence interval of the mean difference are entirely within the equivalence margin. Therefore, statistical equivalence in mean values for bioactivity is established among EP2006 U.S. Neupogen and EU Neupogen.

Similar as bioactivity, we also performed the statistical equivalence testing for content, which is another critical quality attribute for tier 1. The content data points were reported as percentage of the actual protein concentration relative to the target value of 600 micrograms per milliliter.

In the data set we have 20 EP2006 lots, 12 U.S.-licensed Neupogen lots, and 49 EU-approved Neupogen lots. And the equivalence testing results were summarized in similar graphs as what we have for bioactivity. Again, we can see that all 90 percent confidence interval of the mean difference are entirely within the equivalence margin. Therefore, for content we can also conclude statistical equivalence in mean values among EP2006 U.S. Neupogen and EU Neupogen.

That brings me to the end of my talk. In summary, for bioactivity, statistical equivalence in mean values is established among EP2006 U.S. licensed Neupogen and EU-approved Neupogen. For content, we have a similar conclusion. In summary, statistical equivalence testing results support the conclusion that EP2006 is analytically highly similar to U.S.-licensed Neupogen. Thank you very much.

FDA Presentation - Chris Sheth

DR. SHETH: Good afternoon. I'm Chris Sheth, the pharmacology and toxicology reviewer, and I will be covering the FDA's assessment of the nonclinical studies submitted to the application. Since I'll be talking about some of the animal studies submitted to the application, I'd like to reiterate how these studies factor into the overall assessment of similarity.

The first point is that the comparative animal studies may support the similarity of a proposed product to a reference product through an assessment of toxicity and/or PK and PD profiles. However, animal PK and PD assessment will not negate the need for human PK and PD studies.

So moving on to the application under review, the mechanism of action by which G-CSF produces its effects is the same across mammalian species, and the rat is an appropriate research model for studying G-CSF.

This presentation will be centered around the two key animal studies that pharmacology and toxicology reviewed with regards to an assessment of the similarity of EP2006 to EU Neupogen, namely the 006 study in rats, which was a 28-day repeat dose toxicity and toxicokinetic study, and the 004 study, which was a 12-day repeat dose pharmacodynamic study, which evaluated the neutrophil response in rats.

In this presentation, I will use words like "similar" and "similarity" to refer to things being qualitatively similar without regards to prespecified analytical or statistical components. And after addressing these animal studies, I will tell you from my discipline's perspective whether we think these animal studies, in conjunction with the scientific bridge and statistical comparisons you will hear about from my colleagues, support a demonstration of biosimilarity.

Shown here is the design of the 28-day study in rats. Animals were randomized to groups receiving daily subcutaneous doses of either control EP2006 or EU Neupogen at doses between 20 and 500 micrograms per kilogram. Animals assigned to the main study were evaluated for signs of toxicity after 28 days of continuous dosing, and those assigned to the recovery period were evaluated for signs of reversibility or worsening of toxicity six weeks after their last dose. The toxicokinetic animals were evaluated for exposure to G-CSF throughout the 28-day main study.

Here are some of the results for exposure as measured by area under the curve from zero to 24 hours in rats, administered 20 micrograms per kilogram of EP2006 or EU Neupogen.

We can see the mean AUC values hover around 250 nanogram hour per mL at this dose for males and females given either product over the course of the study. Exposure in the rat increased with increases in dose and were similar across the groups receiving 500 micrograms per kilogram as well. However, AUC values for the 20 microgram per kilogram dose are most similar to the human AUC values observed at clinically relevant doses.

Here's a summary of the toxicity results from the 006 study. Specifically, we noted that clinical signs, body weights, and clinical pathology were similar between EP2006 and EU Neupogen groups.

We also noted increases in spleen weight of up to twofold were similar in rats administered either product and were similarly reversible, and microscopic findings of hyperplasia in the bone marrow, liver, lymph nodes, and spleen occurred with similar incidence, severity, and reversibility in rats administered EP2006 as compared to EU Neupogen.

I'd like to move on now to the 12-day pharmacodynamic study that evaluated the neutrophil response in naive and day zero chemotherapy-induced neutropenic rats. The rats received daily subcutaneous doses of control or 10 to 160 micrograms per kilogram of EP2006 or EU Neupogen on days 1 through 4, followed by an 8-day observation period.

Here are what some of the data look like.

We can see both EP2006 in the open squares and EU Neupogen in the closed diamonds produce similar distinctive biphasic increases and absolute neutrophil counts over the course of the study.

Of note is that day zero chemotherapy-induced neutropenia, which was observed on day 1, had recovered by day 2, as shown here by the separation of the G-CSF treated groups from the cyclophosphamide group. The similarity of EP2006 to EU Neupogen is exemplified here by the nearly superimposable neutrophil response curves in that even points that aren't superimposed are still within one standard deviation of one another.

So in conclusion, no discipline-specific residual uncertainties have been identified and that the animal pharmacology and toxicology study submitted indicate that EP2006 is similar to EU Neupogen.

Finally, I'll say that the comparative animal studies were considered in conjunction with the scientific bridge and statistical comparison of EP2006, EU Neupogen, and the reference product, U.S.-licensed Neupogen, in the spirit of the totality of evidence approach to our review, and were found to support a conclusion of biosimilarity. Thank you.

FDA Presentation - Sarah Schrieber

DR. SCHRIEBER: I'm Dr. Schreiber, and I'll be presenting the clinical pharmacology data from the EP2006 BLA submission. During our review, we aim to answer the key question, does the clinical pharmacology data submitted in this BLA support the determination of biosimilarity of EP2006 to U.S.-licensed Neupogen?

Single-dose pharmacokinetic similarity was assessed in study 109 in healthy subjects. Pharmacodynamic similarity was also assessed. In study 109, absolute neutrophil counts were evaluated following single-dose administration in healthy subjects.

In studies 101 and 103, CD34 cell counts were evaluated in healthy subjects following multiple dosing. The applicant included additional supportive single-dose PK and PD studies, as well as a safety and efficacy study.

So to answer the key question, based on the results of these various studies, yes, the clinical pharmacology data support a determination of biosimilarity.

In the next two slides, I'll provide an overview of these studies submitted to the BLA that we considered in our review. There were two studies that used U.S.-licensed Neupogen. Study 109 was a healthy subject, single-dose, PK/PD study, but is considered a key study in our assessment of similarity. It was a randomized, double-blind, two-way crossover study that assessed a 10 microgram per kilogram sub-Q dose.

Study 302 was a randomized, double-blind, active control efficacy and safety study in patients with breast cancer. Study 302 included a PK substudy to characterize the pharmacokinetics of EP2006 and U.S. Neupogen in patients in cycle 1. This PK substudy was not designed to assess similarity.

The remaining studies 103, 105, and 101, were healthy volunteer, single and/or multiple-dose PK/PD studies that used EU-approved Neupogen at various doses. Each study was a randomized, double-blind, crossover study, which is similar to that used in study 109. Specifically, I will present the results of study 103 and 101 that evaluated multiple doses in order to evaluate similarity as it relates to the PD marker, CD34.

The detailed PK/PD study design of study 109 is presented in this graphic. As I mentioned, study 109 was a healthy subject, PK/PD study that used U.S.-licensed Neupogen. The design was a randomized, double-blind, two-way crossover study in 28 subjects. Single doses of 10 micrograms per kilogram sub-Q were administered in each period following a 28-day washout period.

In group 1, subjects received EP2006 first, followed by U.S. Neupogen. Alternatively, subjects in group 2 received U.S. Neupogen first, followed by EP2006. The 28-day washout period was adequate and allowed for G-CSF to be cleared from systemic circulation and absolute neutrophil counts returned to baseline prior to the dose in period 2.

Study 109 had two objectives, single-dose pharmacokinetics and single-dose pharmacodynamics, namely, absolute neutrophil count. For PK, the objectives were area under the curve, or AUC, and maximum concentration, or Cmax. Looking to the time versus concentration profile, you can see that the space below the curve is considered the AUC, and the highest concentration on the curve is defined as the Cmax.

Going back to the objectives, the 90 percent confidence interval for the ratio of the geometric means of the AUC and Cmax should lie within 80 to 125 percent. The ratio is calculated by dividing the geometric mean AUC or Cmax of the test product by that of the reference product.

The range of 80 to 125 percent is a plus or minus 20 percent difference of the log transformed values. When this criteria is met, we conclude that the two treatments are not different from one another. This range of 80 to 125 percent is considered a starting point in the assessment of similarity.

For the PD marker absolute neutrophil count, the objectives were area under the effect curve and ANCmax. And in this case, the 95 percent confidence interval for the ratio of the geometric means should lie within the 80 to 125 percent range for both AUEC and ANCmax. The same principles follow for deriving the ratios that I described for pharmacokinetics.

Before I go into the results of the study, I'd first like to take a moment to describe various aspects of the PK/PD studies. First, we'll start with the study design.

As is described in the draft guidance to industry entitled "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product," for PK similarity assessments, a single-dose, randomized, crossover study is generally the preferred design.

A crossover study design is recommended for products with a short half-life, which is the case with G-CSF, rapid pharmacodynamic response for which an absolute neutrophil count response is observed within 24 hours of dosing, and low incidence of immunogenicity. Given this, a single-dose crossover design for pharmacokinetics and absolute neutrophil count similarity is justified.

Furthermore, a multiple-dose study is appropriate for pharmacodynamic similarity assessments where the pharmacodynamic effect is delayed, which is the case with CD34 response. Therefore, a multiple-dose crossover design for CD34 similarity is also justified.

Next we move to the study population. The use of healthy subjects in the PK/PD studies is justified. Safety in healthy subjects has been established in multiple sub-Q doses up to 10 micrograms per kilogram. There is less variability in both pharmacokinetics and pharmacodynamics due to less confounding by patient factors and treatments.

Healthy subjects are more responsive to G-CSF treatment, in terms of changes in PD markers, than chemotherapy-treated patients due to the fact that they do not have cancer, they've not received prior chemotherapy, they have higher baseline absolute neutrophil count values, and are usually of a younger age than patients. Finally, the mechanism of action is the same regardless of population. For these reasons, healthy subjects are considered a sensitive model to use to assess G-CSF activity.

This slide provides the characteristics of the pharmacodynamic markers that could support biosimilarity assessment. A PD marker used to support assessment of biosimilarity should be sensitive and relevant, have a well-defined mechanism of action, and ideally may also correlate to efficacy.

The pharmacokinetics should have an influence on the pharmacodynamic response. In other words, changes in the dose or exposure would elicit changes in the marker. Of course, the assays for both PK and PD should be validated.

As I previously alluded to, for G-CSF, the pharmacodynamic markers are absolute neutrophil count and CD34 cell counts. In the next few slides, I'll discuss how absolute neutrophil count and CD34 correlate with efficacy, and I'll present the dose-response data for both PK and PD as well.

First I'll start with an absolute neutrophil count. For the category of neutropenia indications for Neupogen, absolute neutrophil count is correlated with duration of severe neutropenia or DSN, which was the endpoint used in clinical efficacy trials.

The panel on the left depicts the absolute neutrophil count levels in patients as correlated with duration of severe neutropenia. This is the U.S. Neupogen cycle 1 data from Sandoz study 302. The X-axis depicts increasing quartiles of the ANC area under the effect curve, and the Y-axis is the duration of severe neutropenia in days.

As the absolute neutrophil count AUEC increases, the duration of severe neutropenia decreases. Given the correlation between absolute neutrophil count and duration of severe neutropenia, we evaluated if a clinically significant difference in DSN between the test and the reference product could be detected by differences in the absolute neutrophil count.

Sandoz study 302 U.S. Neupogen data from cycle 1 was used the simulation. In the figure on the right, the X-axis represents the percent difference in absolute neutrophil count between the test and reference products. The Y-axis represents the mean difference in duration of severe neutropenia between the test and reference.

Using an acceptability limit of plus or minus 20 percent, we can see that this difference in ANC, area under the effect curve, between the test and the reference would translate into a mean difference in DSN of less than plus or minus .2 days, which is represented by the boxed region.

The difference is less than the maximum clinically acceptable difference in DSN between the products, which was determined to be 1 day. Therefore, this analysis shows that using an absolute neutrophil count as a pharmacodynamic marker in PK/PD studies will be sensitive to detect clinically meaningful differences in a proposed biosimilar product.

In terms of endpoints for the mobilization indication, CD34 cell count is a relevant pharmacodynamic marker. Colony-forming unit, granulocyte, monocyte, or CFU-GM, is used as a marker for peripheral blood progenitor cells that promote hematopoietic recovery. CFU-GM and CD34 yields in the leukapheresis products were important endpoints for the approval of the Neupogen mobilization indication. The total number of CFU-GM and/or CD34 cells collected was a significant predictor of complete hematopoietic recovery.

As shown in the figure in the left panel, following multiple 10 microgram per kilogram sub-Q Neupogen doses, CFU-GM in the black circles and CD34 cell counts in the red squares follow a similar time profile. Furthermore, as shown in the panel on the right, CD34 cells correlate with CFU-GM cell levels. Therefore, the effects on stem cell mobilization can be reliably assessed and compared based on CD34 cell counts from PK/PD studies in the assessment of similarity.

Finally, as it relates to the dose. Doses up to 10 micrograms per kilogram appear reasonable for demonstrating pharmacokinetic and pharmacodynamic similarity. The data presented on this slide are from the current BLA. Regarding dose exposure for absolute neutrophil count, an increase in the area under the effect curve of ANC is observed with increasing single sub-Q doses of 1 to 10 micrograms per kilogram in healthy subjects.

Regarding dose exposure for CD34, an increase in the area under the effect curve of CD34 cell count was observed with increasing multiple daily sub-Q doses of 2.5 to 10 micrograms per kilogram. And these last columns depict the dose exposure for single-dose pharmacokinetics over the sub-Q dose range of 1 to 10 micrograms per kilogram. Doubling the dose results in a 2 to 2.8-fold increase in exposure.

Given the observed trend for increase and exposure in healthy subjects following sub-Q administration of doses up to 10 micrograms per kilogram, a G-CSF sub-Q dose of up to 10 micrograms per kilogram appears reasonable for demonstrating PK and PD similarity. To summarize, ANC and CD34 cell counts are both sensitive and relevant markers for which changes in dose elicit changes in the PD response.

Now we come back to the EP2006 submission. Here we have the two Neupogen indication categories, neutropenia and mobilization. The U.S.-licensed Neupogen PK/PD single-dose 10 microgram per kilogram sub-Q study in healthy subjects supports the category of neutropenia indications. Multiple doses were not evaluated in that study, which is needed to support the mobilization indication, so a bridge to the multiple-dose EU Neupogen PK/PD studies is needed to justify the relevance of that data to a demonstration of biosimilarity to U.S.-licensed Neupogen for the mobilization indication.

To this end, a robust scientific bridge using analytical similarity between EP2006, U.S. Neupogen, and EU Neupogen products presented earlier by Dr. Gutierrez was used. Single dose EU Neupogen PK/PD studies were also submitted and are considered supportive in the overall assessment.

Next, I'll present the results from the PK/PD studies. This slide presents the PK and absolute neutrophil count results from the U.S. Neupogen study 109. The panel on the left depicts the time versus concentration profile for pharmacokinetics.

The dark circles represent EP2006 concentrations and the open circles, U.S. Neupogen. Note that the EP2006 concentrations are slightly lower than that of U.S. Neupogen around the Tmax, and this difference in absorption between the products appears related to differences in the buffer systems between the products.

The statistical analysis for both AUC and Cmax met the predefined criteria, where the

90 percent confidence interval for the ratio of the geometric means were within the 80 to 125 percent range.

The panel on the right depicts the time versus concentration profile for the PD marker absolute neutrophil count. Here the profiles are superimposable, and the 95 confidence interval for the ratio of the geometric means for both ANC, AUEC, and ANCmax, are contained within the 80 to 125 percent range.

The results of this PK/PD study support the category of neutropenia indication.

Regarding the mobilization indication, two EU Neupogen studies, 103 and 101, were submitted where multiple sub-Q doses between 2.5 to 10 micrograms per kilogram were evaluated in healthy subjects. For each of the doses, the statistical analysis criteria were met for both CD34, area under the effect curve, and CD34max. As is shown in the table, the 95 percent confidence interval for the ratio of the geometric means were within the 80 to 125 percent range.

Based on the acceptability of the scientific bridge to the EU Neupogen, this data supports the mobilization indication category.

As I noted on the study overview slide, additional sub-Qs, single-dose pharmacokinetic and absolute neutrophil count data from healthy subjects were included in the application that used EU Neupogen. As is shown in the table, single 1 to 10 microgram per kilogram sub-Q doses in healthy subjects met the predefined AUC and Cmax, and ANC, AUEC, and ANCmax criteria, except in 103 where the lower bound of the 90 percent confidence intervals for Cmax at the 2.5 microgram per kilogram dose fell just outside the range at 79.

These results are considered as supportive single-dose pharmacokinetic and absolute neutrophil count data in the assessment of similarity, and the results are consistent with those of study 109 that was conducted using U.S. Neupogen.

Lastly, I'll describe the PK substudy results from the patient efficacy and safety study 302. For characterization of the PK in cycle 1 only, 27 patients from the EP2006 arm, and 27 from the U.S. Neupogen arm were enrolled in this PK substudy.

The study employed a parallel design and, again, was not designed to assess PK and PD similarity. The left panel depicts the 24-hour time versus concentration profile in cycle 1 following the first dose. Again, the dark circles represent EP2006 concentrations and the open circles, U.S. Neupogen.

Cycle 1 EP2006 exposures were generally lower compared to U.S. Neupogen, which is consistent with what was observed in the healthy subject PK/PD studies. The variability in the patient pharmacokinetics was much greater, around 40 percent, compared to healthy subjects, which was less than 20 percent.

Next, let's consider the cycle 1 absolute neutrophil count profile. The time course of the ANC in cycle 1 for the per protocol population is illustrated in the figure on the right and is representative of a typical profile. The nadir was around days 7 and 8, which is expected, and there were no marked differences in the mean ANC between EP2006 and U.S. Neupogen up to day 10.

Of note, the absolute neutrophil count measurements were only made until the ANC recovered or until day 15, whichever occurred first, so following day 10, the ANC in most patients had recovered, and very few patients were required to be followed through day 15 as is noted by the small number of patients, between 4 to 25 per arm, for those assessments on days 12 through 15.

Given these absolute neutrophil count results, coupled with the clinical efficacy and safety results from the study that Dr. Przepiorka will present, we conclude that the slight differences observed in the pharmacokinetics within this patient PK substudy did not appear to translate into clinical meaningful differences.

In final summary, the pharmacokinetic and pharmacodynamic study results support a demonstration of no clinically meaningful differences between EP2006 and U.S.-licensed

Neupogen. The pharmacokinetic and pharmacodynamic study results add to the totality of the evidence to support a demonstration of biosimilarity of EP2006 and U.S.-licensed Neupogen. Thank you.

FDA Presentation - Susan Kirshner

DR. KIRSHNER: Good afternoon. I'm Susan Kirshner in the Office of Biotech Products, and I'm going to talk to you about EP2006 immunogenicity.

People treated with therapeutic biological products may develop immune responses to the therapeutic biologic in the form of antidrug antibodies. Antidrug antibodies can result in severe consequences to the treated patient or subject, including loss of activity to endogenous counterparts leading to deficiency syndromes, which in the most severe cases can become autoimmunity, hypersensitivity reactions including anaphylaxis, and loss of efficacy of the biologic therapeutic product.

Therefore, establishing similarity in the immunogenicity profiles of the proposed biosimilar and the reference product may be an important component of the totality of evidence supporting the demonstration of biosimilarity.

A 2014 publication by Pulsipher et al provided results from a prospective 5-year study of 6,768 peripheral blood stem cell donors who were treated with G-CSF and 2,726 bone marrow donors who were not treated with G-CSF. The results of that study showed that peripheral blood stem cell donors were not at increased risk for developing an autoimmune disease when compared to bone marrow donors.

In addition, FDA is unaware of reports of neutralizing antibodies to G-CSF products. Therefore, the literature indicates that G-CSF products are low risk for causing antidrug antibody-related severe adverse effects.

Sandoz performed a number of studies in which the development of antidrug antibodies to EP2006 or a comparator product was evaluated. Study EP06-302 had parallel arms in which patients with cancer were treated with multiple doses either of EP2006 or a comparator product.

In study EP06-302, none of the treated patients with cancer developed antidrug antibody. That study was important because the multiple-dose, parallel arm study design allows us to understand the relative immunogenicity of EP2006 and the comparator product.

Sandoz also performed four single and multiple-dose studies evaluating pharmacokinetics, pharmacodynamics, and immunogenicity of EP2006 and comparator products in healthy subjects. None of the treated subjects in those studies developed antidrug antibodies. Those studies provide information on the immunogenicity of EP2006 in subjects whose immune systems were not compromised by chemotherapy treatment.

Sandoz also provided antidrug, antibody results for patients with cancer treated with EP2006 in a multiple-dose, single arm study with no comparator. None of the patients who participated in that study developed antidrug antibody. Results from that study help support the findings of low rates of antidrug antibody development observed in the comparative studies.

The results from immunogenicity studies support a demonstration of no clinically meaningful differences in immune responses between EP2006 and U.S.-licensed Neupogen. Thank you.

FDA Presentation - Donna Przepiorka

DR. PRZEPIORKA: I will present FDA's analysis of study EP06-302, limiting it to the critical efficacy endpoints and safety endpoints, the analyses performed to assess the risk of hypersensitivity, and how these analyses inform our conclusions regarding the biosimilarity of EP2006 and U.S.-licensed Neupogen.

Protocol 302 was a randomized, double-blind, active control trial. Eligible patients had breast cancer and were to receive six cycles of docetaxel, doxorubicin, and cyclophosphamide as adjuvant or neoadjuvant therapy. The combination of the dose as shown here has a median 29 percent rate of febrile neutropenia, which is acceptable for the purposes of testing a leukocyte growth factor.

Chemotherapy was given day 1 of each 21-day cycle, and growth factor was given daily from day 2 to neutrophil recovery. Subjects were randomized equally to one of four arms, receiving either EP2006 for all 6 cycles as in arm 1, U.S.-licensed Neupogen for all 6 cycles as in arm 4, or an alternation of the growth factors over the 6 cycles.

The primary analysis of the primary endpoint of the protocol -- rather, the primary endpoint of the protocol was the duration of severe neutropenia in cycle 1 specifically. Cycles 2 to 6 were not used in the assessment of the primary endpoint.

For purposes of the assessment of the primary endpoint, the duration of severe neutropenia was defined as the absolute number of consecutive days with an absolute neutrophil count or ANC less than 500, and the difference in the duration of severe neutropenia was determined by analysis of covariance in the per protocol population.

The objective of the design as planned originally was to establish non-inferiority using a

1-day margin; 218 subjects were randomized; 14 subjects had major protocol violations in cycle 1 and were excluded from the per protocol population. For the remaining 204 subjects, the demographic characteristics were largely balanced between treatment groups as described previously by the applicant.

The mean duration of severe neutropenia in cycle 1 was 1.17 days for the 101 subjects treated with EP2006, and 1.2 days for the 103 subjects treated with Neupogen. The calculated difference in DSN was 0.04 days.

The applicant indicated that the lower one-sided 97.5 percent confidence interval was minus 0.26 days, and since this was within the 1-day margin they concluded that the non-inferiority was demonstrated.

However, the guidance published by FDA in February 2012 states that clinical studies should be designed such that they can demonstrate that the proposed product has neither decreased nor increased activity compared to the reference product, and FDA determined that the one-sided analysis performed by the sponsor was not sufficient for the assessment of EP2006 for biosimilarity.

The agency instead conducted an equivalence analysis of the primary endpoint using a two-sided 90 percent confidence interval. Upper and lower margins for this analysis were both 1 day. And during the question period, my statistical colleagues will answer or address the question on the table regarding the choice of 1-day for both the upper and lower margins for this analysis.

The calculated 90 percent confidence interval was minus 0.21 days to plus 0.28 days with both sides of the interval being within the 1-day margin on each side. The conclusion was that equivalence was demonstrated.

For the analysis of safety endpoints, FDA used the safety population, which was all subjects who received at least 1 dose of study drug and had a subsequent safety assessment. Two comparisons were made. The first was limited to events in cycle 1. This maximized the denominator and allowed for greater sensitivity in the assessment.

The second comparison included safety events across all 6 cycles for subjects in arm 1 versus arm 4, the two arms, which utilized the same growth factor in all cycles. This allowed for a comparison over a longer term use of the study agent.

It should be noted that since the trial was not designed to test equivalence of safety endpoints with statistical rigor, conclusions were based instead on visual examination of descriptive results.

This table shows a breakdown of the major safety events for each comparison. There were no substantial differences between treatment groups for treatment emergent adverse events or related treatment emergent adverse events.

There was 1 fatal event on study, a pulmonary embolism in the setting of pre-existing rheumatic heart disease in cycle 1, and this was considered unrelated to the study agent. In fact, there were no related serious adverse events and no related fatal events reported for either treatment group.

The briefing document provides lengthy tabulations of adverse events terms, which, as discussed by the applicant, showed no substantial differences between treatment arms.

The agency identified 2 specific adverse events for closer scrutiny. The first was musculoskeletal pain, chosen because these events are the most common toxicity of leukocyte growth factors. The second was injection site reactions assessed to ensure that the difference between the EP2006 and Neupogen formulations did not impact the risk of local reactions.

In order to capture all similar events, group terms as defined in the footnotes of this table and specific for this protocol were used for this comparison. The results showed no substantial difference between treatment groups and the rates of musculoskeletal pain events or injection site reaction events.

Lastly, the agency assessed events potentially denoting hypersensitivity reactions using standardized MedDRA queries or SMQs. There were no related adverse events reported with allergic reaction terms specifically. As such, the narrow and algorithmic SMQs, which emphasize specificity were not informative.

The table here shows the comparisons for the broad SMQs, anaphylactic reactions, and hypersensitivity. The broad SMQs include the individual signs and symptoms that might occur with a hypersensitive reaction, increasing the sensitivity in case there was underreporting of specific allergic terms. The analysis showed no substantial difference between treatment groups for either of the broad SMQs.

In summary, FDA's analysis of protocol 302 showed no clinically meaningful differences between EP2006 and U.S.-licensed Neupogen with respect to DSN in cycle 1, and safety outcomes are similar for patients treated with either EP2006 or U.S.-licensed Neupogen.

These results support the demonstration of biosimilarity based on the analytical comparisons in the assessment of pharmacokinetic and pharmacodynamic parameters in healthy subjects as discussed by the previous reviewers.

Dr. Deisseroth will now present the overview of the FDA findings and the introduction to the questions.

FDA Presentation – Albert Deisseroth

DR. DEISSEROTH: I will now provide a summary of the FDA findings. The review of the CMC studies showed that EP2006 is highly similar to U.S.-licensed Neupogen. A scientific bridge was established to justify the relevance of clinical data obtained from studies using EU-approved Neupogen to support a demonstration of biosimilarity to U.S.-licensed Neupogen.

The nonclinical studies show that EP2006 is similar to the reference product, U.S.-licensed Neupogen. Clinical pharmacology studies show that they support a demonstration of no clinically meaningful differences between EP2006 and

U.S.-licensed Neupogen.

Immunogenicity studies show that there were no clinically meaningful differences in terms of antidrug antibodies between EP2006 and U.S.-licensed Neupogen.

The clinical studies, 302, which was a comparison of DSN duration of severe neutropenia between EP2006 and U.S.-licensed Neupogen support the conclusion that there are no clinically meaningful differences between EP2006 and U.S.-licensed Neupogen.

Four of the five indications for which U.S.-licensed Neupogen is approved relate to the effect of Neupogen on the levels of neutrophils in the peripheral blood, and one of the five indications relates to the effect of Neupogen on the level of CD34 positive stem cells in the peripheral blood.

As discussed many times today, it is well-documented that binding of Neupogen to the granulocyte colony-stimulating factor receptor on cells is the first step of Neupogen-mediated neutrophil differentiation and proliferation, as well as in CD34 positive stem cell mobilization.

Thus, there is scientific justification for extrapolating the clinical data submitted by Sandoz to support a determination of biosimilarity for each condition of use for which licensure is sought. The data submitted by Sandoz demonstrate that EP2006 is highly similar to U.S.-licensed Neupogen and that there are no clinically meaningful differences between the two products.

In addition, the totality of evidence supports that EP2006 should be granted licensure as a biosimilar product for all five of the indications for which U.S.-licensed Neupogen is licensed.

This slide summarizes two questions for which the FDA is requesting discussion by the advisory panel. Question number 1, does the committee agree that EP2006 is highly similar to the reference product U.S.-licensed Neupogen, notwithstanding minor differences in clinically inactive components?

Question 2, does the committee agree that there are no clinically meaningful differences between EP2006 and U.S.-licensed Neupogen?

This slide summarizes a single question for voting by the advisory committee. Does the committee agree that based on the totality of evidence, that EP2006 should receive licensure as a biosimilar product for each of the five indications for which U.S.-licensed Neupogen is currently licensed?

This concludes the FDA presentation.

DR. ARMSTRONG: Thank you very much.

It's 12:42 right now. We will break for lunch. We will reconvene in one hour at 1:45, at which time we'll continue with clarifying questions to the FDA. Panel members, please remember that there should be no discussion of the meeting topic during lunch amongst yourselves or with any members of the audience. Thank you.

(Whereupon, at 12:42 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:45 p.m.)

Clarifying Questions to the Presenters

DR. ARMSTRONG: We're going to be taking clarifying questions to the FDA from panel. Please remember, for the panel members, to state your name for the record before you speak. If you can, please direct questions to a specific presenter. Also realize that there were a number of people from FDA presenting, and they each have a separate slide set. So if you can let Caleb know which slide -- if you're going to refer to a slide, which slide set it is, it will help him be able to bring those up for us. Dr. Waldman?

DR. WALDMAN: So this is, I guess, for Dr. Schrieber. And I think it was her slide 19, the ANC time course in cycle 1 for study 302. Yes, that one. So this matches the data that's in the Sandoz file, except for the numbers at the bottom of the graph. So the EP and Neu, those numbers that extend out there, they're different.

The reason that it caught our attention, we were wondering why they were different, is because this shows a difference in the last 4 or 5 days of the cycle for people who don't recover in one treatment versus the other, while in the Sandoz data -- which probably we'd want to see, is figure 21 from their file -- it shows a different number of people in these groups, and they're equivalent. I mean they're almost dead-on to each other.

So I was wondering -- I think we were wondering where the difference in the data lie. Surprise.

(Laughter).

DR. ARMSTRONG: This is a question for you.

DR. WALDMAN: Welcome back. This is all about you.

DR. ARMSTRONG: The question was about the difference in the numbers on the bottom of the slide here and in the Sandoz slide here.

DR. WALDMAN: You see, Zarxio and Neupogen, days 12, 13, 14, and 15. So 13, 14, and 15, 6/7, 5/4, 4/2. If you look at the -- so that's days 13, 14, 15. If you look at the other data, 13, 14, and 15, it's 16/9, 15/6, 14/4.

So what's catching our attention here -- and it's important which data is the right data because one set of data shows a difference in the last three or four days in the two groups and the other data doesn't. Does that make sense?

DR. SCHRIEBER: So our statistician pulled this data. This is the per protocol population per our analysis.

DR. WALDMAN: I believe that the Sandoz packet also says it's the per protocol analysis.

DR. SCHRIEBER: Our statistician hasn't returned yet, so I'd have to defer.

DR. WALDMAN: Totally get it.

DR. ARMSTRONG: Is there any chance that Sandoz can explain the difference in the numbers?

DR. SCHRIEBER: There she is.

DR. LEE: [Inaudible - microphone off] -- for population, and less than mean and standard deviation for two groups.

DR. ARMSTRONG: I think it's the number of patients on the bottom.

DR. LEE: Yes, it's the number of patients in the --

DR. ARMSTRONG: Yours is different than the Sandoz. Why is it different?

DR. LEE: I used the Sandoz data.

DR. WALDMAN: You guys see the difference that I'm talking about? And it's significant.

So the reason that we're dwelling on this is that if you use those numbers as one functional endpoint, then there's a difference in recovery of absolute -- of the neutrophil count over time, for the two treatments.

DR. DEISSEROTH: Madam Chairman, may I make a comment?

DR. ARMSTRONG: Thanks.

DR. DEISSEROTH: So these are complex curves, and the clinically relevant -- the domain of the curve that is relevant to biosimilarity and to clinically meaningful differences would be the nadir and then the rate of recovery from the nadir. And the one thing you'll notice about the profiles in both the Sandoz and agency representation is that even at the end, for the Sandoz product, the absolute level of the neutrophil count is 5,000, which is way above what is required to restore normal protective function of the circulated myeloid cell mast.

So one could approach this question by saying, well, it may not be -- even if there were a difference in the data representation there, the contour of the slides suggests that we're out of the range of clinically meaningful differences, because this is post-recovery.

As I guess implied by the reference to the number of patients that remains at that time, those are the slow recoverers. And we don't know if those are statistically different contours, and the contours are all above 5,000.

So is that a clinically meaningful difference?

DR. WALDMAN: So that's the question here. Is that a clinically meaningful -- and that's the question that was being asked earlier this morning;

what is clinically meaningful and what's not? I don't know if this is clinically meaningful, but I could make a hypothesis to you that the PK is a little bit different, even in the healthy volunteer studies. And the patients here, at the terminal phase of the cycle, have a slower recovery time and that there's more people that don't recover in one treatment than the other. And it happens to be the same treatment that has a slightly different PK.

So you could piece together a hypothesis that says they're not exactly the same drug. They're not behaving exactly the same.

DR. DEISSEROTH: But is that behavior above the level of 5,000 absolute neutrophil count going to result in clinically meaningful differences?

DR. WALDMAN: Well, you have some people there that aren't above 5,000. I'm looking at the standard deviations, the error measurements. You have people that are down near zero.

DR. DEISSEROTH: In both curves.

DR. WALDMAN: Well, I take your point. I think it's something for us to discuss.

DR. DEISSEROTH: Right.

DR. WALDMAN: Or at least make note of.

DR. DEISSEROTH: Right. So I would just point out that in terms of the action of filgrastim, it's the rate of -- well, the first peak is repartitioning between the marrow and the peripheral blood, and the second peak is the result of hematopoietic recovery after chemotherapy. And once you get above 1,000 or 1500, you're out of the clinically relevant neutropenia range. And so we're way above that. So that's my point.

DR. ARMSTRONG: We have a comment about this from Dr. Fojo, and then we would actually ask the statistician who spoke to please give your name into the microphone, just regarding this topic.

DR. HILLARD: Yes. Hi. This is Randy Hillard. I had a --

DR. ARMSTRONG: I'm sorry. Can you hold on one second?

DR. HILLARD: Okay. Oh, sorry.

DR. ARMSTRONG: And if this is regarding this question, I'll get to you next. But Dr. Fojo and -- thank you.

DR. LEE: My name is Kyung Lee.

DR. ARMSTRONG: Thank you.

DR. FOJO: So this is Tito Fojo. We're both thinking the same thing, that this is something that's telling you that it's quite not the same as Neupogen. I think that's what it's saying. And the problem is that we give so much Neupogen, and it's so effective, that even something that is not quite like Neupogen is still going to be clinically -- you know at above 5,000, and that's what you're getting at.

So clinically it ends up no difference, but that doesn't mean that the drugs might not be different at some other level. And I think that it has to do with the formulation, and the pH, and the buffer, and their data clearly shows that.

So does it affect -- is it clinically meaningful? No. So you're right, but I think we're right to be concerned that this is not the same thing.

DR. DEISSEROTH: Well, I think you're right,

too, that it may relate to recovery --
DR. FOJO: Right.
DR. DEISSEROTH: -- or absorption and exposure due to the differences of absorption.
DR. FOJO: Right.
DR. DEISSEROTH: But those differences in a randomized trial that we're observing --
DR. FOJO: We agree with that.
DR. DEISSEROTH: -- could be just fluctuation imbalance.
DR. FOJO: We agree with that. And actually, there's --
DR. DEISSEROTH: And it's out of the range of clinically significant events.
DR. FOJO: Yes. And Sandoz has in table 21 some data that sort of I think puts our concerns at ease, which is those in DSN categories greater than or equal to 3 days, and for all four groups, it's the same, 10 percent give or take.
DR. DEISSEROTH: Right.
DR. FOJO: So clinically it's not meaningful, but --

DR. DEISSEROTH: Yes, clinically the two molecules produce --

DR. FOJO: Right, but they're different, they're not --

DR. DEISSEROTH: -- a DSN that is miniscule differences at .04 days.

DR. FOJO: Yes, we agree. I think we agree with that.

DR. DEISSEROTH: That's the key takeaway.

DR. ARMSTRONG: Dr. Hillard?

DR. HILLARD: Yes. Randy Hillard. If I understand correctly, if you go back to the last slide, I don't think there's a statistically significant difference at any one of these points there. Is there? And although we have three of them in a row that the green line's lower than the purple line, none of those, if I read this correctly, are statistically significant differences. So I'm not sure we should consider them.

Did I get that right?

DR. FOJO: If I could say something? Tito

Fojo. What we're saying is that there's more patients requiring prolonged administration with the Sandoz drug than with Neupogen. That's where the difference is. Once you're giving it, you're going to get comparable counts, just that it required longer administration to sustain them. They weren't recovering to as high as quick.

Am I speaking for you?

DR. HILLARD: I'm not sure that's what the data says. Could you give us a statistical opinion?

DR. COLE: Chip Cole. I can comment.

DR. ARMSTRONG: Yes, please, go ahead.

DR. COLE: What I'm seeing are potentially a subset of patients that it's taking longer in one arm. But please remember, this is not a very large randomized study, so it could be just some imbalance by chance. We can't rule that out.

DR. DEISSEROTH: Right. These are patients who have cancer. They're older than the normal volunteers, so they have decreased marrow cellularity and different response. And they may have had exposure differences that we don't know about. So to address this, we'd have to do another trial I think.

DR. ARMSTRONG: This is Deb Armstrong. I would just point out that I believe that the treatment stops once the ANC hits 10,000, and the lines are really together until it hits 10,000. So where it separates, they're not getting treatment.

DR. DEISSEROTH: So the administration stops right when -- by two criteria, 3 days, 3 consecutive days of a thousand or greater, or 1 day of 10,000.

DR. ARMSTRONG: I had a question, and this is actually for the first presenter, Dr. Gutierrez-Lugo. And it's slide, I think, 15. I had some questions about -- so EP2006, you analyzed two lots of EP2006, one that is sometimes called commercial and one that's sometimes called clinical.

The presenter talked about two different drug names, one from Europe and one from the U.S. We have two different Neupogen, one from the U.S. and one from the EU. And the question I have is that in at least a couple of the analyses you did, you compared the clinical and the commercial EP2006. So can we assume that all of the EP2006 is equivalent or can we not make that assumption?

DR. GUTIERREZ-LUGO: What we can say is that the EP2006 clinical drug product is comparable to the EP2006 proposed commercial product. And by comparable means, they have highly similar quality attributes. The pre, the clinical, and the commercial.

DR. ARMSTRONG: So in this setting, the clinical is what would be proposed for use in the United States?

DR. GUTIERREZ-LUGO: The clinical is what was used in the clinical studies and is comparable to what is being proposed for commercialization in the U.S.

DR. ARMSTRONG: And that's potentially quite important because if these are essentially equivalent, you have data on over 7 million administrations of this product, which makes the safety issue pretty robust.

DR. GUTIERREZ-LUGO: Yes, the demonstration of comparability between the clinical and commercial product was very important.

DR. ARMSTRONG: Thank you.

Dr. Neville?

DR. NEVILLE: Mine was answered, thanks.

DR. ARMSTRONG: Dr. Mager?

DR. MAGER: I wanted to go back to the slide where we were looking at the ANCs. I think this is quite common when you see a very tight overlap under immunosuppressive conditions, to see very tight data in the beginning of the pharmacodynamic curves, and then start to see considerable variability at later time points during recovery. And oftentimes, that's due to inter-subject variability and system parameters as opposed to drug specific parameters.

So given the tightness of the overlap in 109, and given the tightness of the overlap in this study up until day 10, I would hypothesize that almost all of that variability at the end is probably due to system differences as opposed to differences in PK/PD properties.

I was wondering if the pharmacometrics group approached this with a modeling exercise to see if they could assign variability to any of these particular terms. And I don't mean to imply that modeling is necessary to make the decision, nor would I imply that modeling would be definitive in this case, but could be used to support the hypothesis that it's system related as opposed to drug related.

DR. MARATHE: I'm Anshu Marathe from the pharmacometrics division. To answer your question, no, we have not used any modeling approach to be able to discern whether the initial part of the curve is reflective more of the PK/PD properties versus the latter part of the curve is mostly, as you call, system properties. We haven't done that for this particular application.

DR. ARMSTRONG: Does that answer your question?

DR. MAGER: Yes. Thank you.

DR. ARMSTRONG: Okay, thank you.

Dr. Stroncek?

DR. STRONCEK: I have a couple questions, one related to this study. If this was a post-bone marrow transplant study, I think what people would do is look at time for neutrophil recovery. They wouldn't plot it as absolute neutrophil count, so they'd have percentages of patients that had met their criteria for recovery over time. And I think maybe that would be the more appropriate analysis here to see if there's a statistically significant difference as far as recovery.

DR. DEISSEROTH: So to answer your question, if you look at the curves, the rate of recovery to 1,000, 1500, 5,000, and even 10,000, is identical in the two curves, the rate of recovery, which is from the nadir at day 7 to day 10 or 12.

So I think the recovery behavior of the two curves are coincident. It's just that how long that -- we have the confounding factor of patients ending at different -- stopping -- becoming non-participatory in the follow-up because they've reached a point at which the Neupogen or EP2006 administration stops by protocol.

So it's not a perfect data set to address anything beyond day 10, where the patients appear to be similar in number between the two drugs. So I think as far as using this data, we probably should depend heavily on time up to the 10 days at which the numbers of patients appear to be equivalent.

DR. ARMSTRONG: Dr. Fojo?

DR. FOJO: Tito Fojo. So you promised that you would explain why the 1 day, or where that 1 day came from, or what the rationale was for the 1 day, that someone in the group would do that.

DR. DEISSEROTH: Yes. Dr. Gwise will start off.

DR. GWISE: Good afternoon. My name is Thomas Gwise. I'm the deputy director of the Division of Biometrics V. So where did 1 day come from? So ideally, the FDA would like to use a stepwise approach in evaluating biosimilars, as was discussed in Dr. Christl's presentation.

If that stepwise approach is followed, then the questions in the subsequent studies can be designed based on the information provided in the preliminary studies. Here, FDA was presented a non-inferiority study, and, as was mentioned before, we are specifically interested in equivalence or similarity.

So where did the 1 day come from? We have the data, and considering the treatments that were given, there were the three drugs, and we see the effect size is about 6 days, so the 1 day is approximately 20 percent of that effect size. And this is a conservative limit, and it's consistent with what we've seen in the literature.

So we believe this conservative margin, both upper and lower, is reasonable and applicable in this situation. And the important point to note is that the difference seen in the study is miniscule. So the margins in this case are sort of just an added look, and that basically explains where the 1 day comes from.

DR. DEISSEROTH: Right. Dr. Gwise, was -- the differences in the DSN and the primary endpoint, were miniscule, so that the margin selection really is not as important. Although he's given you the rationale, the fact that the DSN was .04 days lessens our interest in selection, although we would have preferred to have bioequivalence. So that's the conservative approach that we took, chemotherapy, three drugs, effect size 5.8 days at 80 percent, 1 day.

DR. ARMSTRONG: Dr. Fojo?

DR. FOJO: To me it seems arbitrary, and that's okay. You know, it is what it is. Actually, it turned out to be at 1.0 -- 1.17 -- and even better than Neulasta, which is where the 6 days comes from --

DR. DEISSEROTH: That's right.

DR. FOJO: -- which is what bothered me to begin with. Right.

DR. DEISSEROTH: So we wanted to reassure that --

DR. FOJO: And I'm not asking it as much for this, since this is sort of the first one coming before the FDA. Is that going to be what will always be the case? It would be better if there was something better than, "Well, we like 20 percent. Why not?"

DR. DEISSEROTH: No, we'll take each drug, each product, one-by-one, and look at the properties of the drug, the patient population, and come to a conclusion about margins, so it will be individualized. Among the filgrastim products, it may depend on the chemotherapy combination used and the effect size that is generated by Neupogen, given that intensity of chemotherapy.

So we would like to focus on Zarxio here rather than trying to make broad statements about what's going to happen in the future that's going to be -- as Dr. Christl said, one size does not fit all.

DR. ARMSTRONG: Dr. Cole?

DR. COLE: One of the things I always enjoy seeing from FDA when we come to these meetings is a series of analyses that pick apart the sponsor's suggestion that the drug should be licensed. And I was asking this because this particular presentation didn't seem to go into the robustness so much for the primary endpoint of the clinical trial. And I think it's important because we are seeing some minor differences in the analytical results on PK, for instance.

So I'm questioning whether there was any kind of analysis of the robustness of this .04 day difference based on severe neutropenia, and this is in slide 5 of the FDA presentation on clinical trial review.

For example, what if you looked at another definition for severe neutropenia, are the things still lining up well, or, is it possible to look at the total DSN over all cycles in the two continuous treatment arms, and if that kind of data's available just to sort of investigate the robustness of this a bit.

DR. DEISSEROTH: I can start.

DR. LEE: My name is Kyung Lee, at division of V, biostatistics. We looked at the [indiscernible] using different analyses. We look at the normalization assumption, and it wasn't valid, so we look at the negative binomial distribution. And also we look at the bootstrap confidence interval, and those results were similar. So we thought it was robust.

DR. COLE: I was asking more about the definitions for the primary endpoint primarily. So like could you change or modify the definition of what constitutes serious neutropenia and severe neutropenia, and if changing that definition alters these results at all.

DR. DEISSEROTH: So duration of severe neutropenia is an endpoint for filgrastim trials, clinical trials, with which we have long experience, over maybe 12 years of experience with multiple trials and approvals. And it appears to be predictive of a good surrogate for febrile neutropenia infections and hospitalizations. And so it's an endpoint that has served us well.

The secondary endpoints, hospitalizations, infections, febrile neutropenia, also were not significantly different. So we not only had duration of severe neutropenia, but secondary endpoints of incidence of febrile neutropenia, hospitalizations and infections. They weren't different either. And those are also endpoints that have been used since 1991 when the first filgrastim product was approved, Neupogen.

So the coincidence of the results, the lack of significant differences across multiple endpoints in the trial, created the impression that this was a robust finding.

DR. COLE: Thank you. Nevertheless, I think some look at the robustness to a change in definition is certainly an appropriate thing to look at and would have been helpful. The other question I had was whether there was an analysis of all of the cycles, perhaps restricted to the continuous treatment arms, so that we could look at what more exposure to the drug did in this particular trial.

DR. PRZEPIORKA: This is Donna Przepiorka, the clinical reviewer. The DSN, per se, was not measured in every cycle, but time to recovery from nadir was, and they were identical in all of the cycles.

DR. COLE: Thank you.

DR. ARMSTRONG: Dr. Neville?

DR. NEVILLE: I just wanted to go back to Dr. Fojo's question because, I apologize, I'm still a little stuck. The 1 day was what was considered clinically significant because -- that was my understanding in the reading. And it's one thing if it's statistical, but I'm hard-pressed to understand still how we came up with 1 day.

Great for this drug that they're close, but I agree, yes, it's a case-by-case basis, but I'm not understanding the rationale.

DR. DEISSEROTH: With the chemotherapy regimen that was used, doxorubicin, docetaxel, and cyclophosphamide, multiple publications have shown that without growth factor support, the duration of severe neutropenia, defined as less than a thousand, or severe neutropenia less than 500, was 7 days without growth factor, and with growth factor, 1.4 days.

So this creates what we consider to be the effect size, which is the number of days of severe neutropenia, which are reduced by the use of the growth factor, and that's 5.8 days.

The reason that we use this threshold of 500 or 1,000 is that a very important paper by Gerald Bodey, back in the '70s, indicated that the risk of infection and mortality is directly dependent on the level of the neutrophil count. The lower it is, the higher the risk.

So the threshold of 500 and a thousand, severe neutropenia less than 500, is accepted as the level below which the incidence of clinically significant infectious complications will increase. So once patients recover to 500, they're going to have a low incidence of infection.

So that is the origin of the choice of severe neutropenia. And then the effect size that is generated by the chemotherapy, which means the days of reduction of the severe neutropenia duration without growth factor and with growth factor, is the effect size.

Now, I have to agree with Dr. Fojo that it's arbitrary. We chose 80 percent as a threshold of acceptability. But to defend that arbitrary selection, it's a very conservative margin rather than something like 50 percent. And so it's a high bar.

DR. JENKINS: Yes, this is John Jenkins. If I could add to that, we have a non-inferiority guidance that we published a couple of years ago. While we're talking about equivalency here, many of the same principles apply. And we say in that guidance that selection of the margin, the non-inferiority margin, is highly based on clinical judgment.

So I think what you're hearing is that the effect size is large, it's about 6 days, and based on clinical judgment -- and people can disagree on what is a clinically meaningful difference in that effect size -- we selected 1 day. We could have selected half a day. It's a clinical judgment decision. There is no absolute approach.

There are some situations where we have accepted a 50 percent preservation of the effect of the active control as being the margin that we're willing to accept in non-inferiority trials. Sometimes that's due to pragmatic concerns, that if you go smaller than that, you have a trial that you cannot achieve the numbers needed to exclude that difference. We also don't just look at the confidence intervals, we look at the point estimate as well. So it's a clinical judgment.

DR. NEVILLE: Thank you.

DR. DEISSEROTH: Yes. Another piece of information is that from the data that we have been looking at inside, a difference of 1 day in duration of severe neutropenia translates into a 10 percent difference in febrile neutropenia, which we consider to be below the limit of clinically significant. We have to have a limit.

So the fact that 1 day in duration of severe neutropenia generates such a small difference in febrile neutropenia was also reassuring and contributed to the thesis that we were selecting a very conservative margin. That was paramount in our considerations.

DR. NEVILLE: That's helpful. Thank you. I wasn't criticizing 1 day; just trying to understand how we got there. So I appreciate it.

DR. DEISSEROTH: Yes, it's -- as I say, we're going to be looking at each one of these, certainly filgrastim applications, which may differ in terms of the chemotherapy that was used or the patient population. And across the entire biosimilar program, you're going to see a vast difference in issues cropping up. And so, we have to tailor the -- try to use the standards to generate responses to an application. So it's going to be drug and application specific.

DR. ARMSTRONG: Dr. Liebmann?

DR. LIEBMANN: Jim Liebmann. I have a question about dosing of the drug. Most of the studies, in fact I think all the studies, the data that we've looked at, the dosing has been based on a microgram per kilogram basis. And it's been stated that the drug, if it's approved, is going to be packaged the same way Neupogen is currently approved, which is to say in 300-microgram or

480-microgram vials.

Practically speaking, most patients get 300 micrograms or 480 micrograms. So if they're less than 60 kilograms, they get 300, and if they're more they get 480, which means that the vast majority of patients get dosed at higher than 5 micrograms per kilogram in real clinical practice.

Your study 301 dosed patients that way, and that had 170 patients with breast cancer. I know that comparing studies is always hazardous, but was there any difference in recovery of blood counts or prevention of neutropenia with that kind of dosing compared to the dosing that we're seeing in study 302?

DR. DEISSEROTH: I think 301 was a non-comparative study, as you know. It was just --

DR. LIEBMANN: I know. That's why I'm wondering about the recovery of counts as compared to the results in 302.

DR. DEISSEROTH: We'll ask Dr. Przepiorka if she conducted an analysis of that.

DR. PRZEPIORKA: No, we did not conduct an analysis looking at recovery between protocols, is the short answer.

Open Public Hearing

DR. ARMSTRONG: All right. We're going to move on now to the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances, and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. MCNEELY: Yes, my name's Larry McNeely. I'm policy director with the National Coalition on Healthcare. The National Coalition on Healthcare is a broad-based coalition of national organizations representing healthcare providers, consumers, patients, payers, purchasers, the whole swath of our healthcare system.

Our coalition strongly supports innovation in biologic medicines. It's made treatment and healing possible for patients in ways not imaginable before. But without effective, generic, biosimilar and interchangeable competition, innovative biologic medicines are often simply unaffordable. The reality is that one study found that the average daily cost of a brand name biologic is approximately 22 times greater than that of a traditional drug.

Unchecked growth in these already high costs is not only a barrier for patients like the folks suffering from neutropenia that this drug would help address, it's a systemic threat to the sustainability of our broader health system and the affordability and ability to access care.

A recent study in health affairs by Aitken, Berndt and Cutler found the U.S. average annual health spending growth from 2002 to 2007 was about 16 percent for biologics compared with 3.7 percent for traditional drugs, so taking a broader portion of our drug spend.

We know how to mitigate this systemic challenge. It involves real competition, and we've seen it in the generic space for chemical drugs, and we know that it can work in this case. A recent study by Express Scripts found that availability of just two biosimilars, Sandoz's Zarxio and Celltrion's Remsima, would save U.S. patients and payers nearly $22.7 billion between now and 2024.

So that is all to say, make a really good case why the National Coalition on Healthcare, consisting of over 80 national groups, supports the approval of biosimilar interchangeable biologics like the ones being considered by the committee today.

I should state that neither myself or my organization has a direct financial relationship or anything to disclose with the sponsor. Thank you.

DR. ARMSTRONG: Thank you. Speaker number 2?

MR. JOHNSTON: Good afternoon. Thanks for the invitation to be here. My name is Gordon Johnston. I'm speaking on behalf of the Generic Pharmaceutical Association. And for the record, I'm supported by GPHA today and don't have any conflicts on this matter.

Before I begin, let me just state, as Dr. Woodcock said, this really is a historic advisory committee meeting. It's historic not only for FDA as it considers approving its first biosimilar product, but more importantly, for the American patients. Biologics are often the only lifesaving treatment for some of the most severe diseases suffered by patients. Biosimilars can help address this need.

In 2010, the law gave FDA the authority to approve biosimilars, and as we heard this morning, manufacturers must demonstrate that their product is highly similar with no clinically meaningful differences.

In this law, FDA was granted an important authority, and that is the discretion to allow it to request any information that it deems necessary to satisfy the scientific requirements on a case-by-case basis. Therefore, as much information that might be needed to support approval can be requested to support a biosimilar approval.

In making these determinations, the agency relies on the same scientists that assess applications for new biological products and who are experienced with the product and the product class represented by the biosimilar.

Critical information for biosimilars is derived from extensive characterization and comparison of structural and functional characteristics using state of the art analytical tools, as well as clinical studies. This allows the agency to make that evaluation based on the totality of the evidence. This approach is fundamentally the same as the approach used when changes are made to innovator products after approval.

When changes are made to the reference product, they use analytical studies, and required clinical studies to support those changes. This information is then extrapolated typically to all indications that the product is approved for. Likewise, GPHA believes that this is a well-established principle that applies equally to biosimilars as justified by appropriate data.

So in summary, in a short 3 minutes, GPHA thanks FDA again for sponsoring this hearing. Biosimilars have been used safely in other highly regulated regions of the world. And likewise, FDA's high standards will assure the safety and efficacy of biosimilars for patients in the United States. We look forward to FDA's ongoing evaluation and approval of biosimilar medicines in the U.S. Thank you.

DR. ARMSTRONG: Thank you. I invite speaker number 3 to come up, and please state your name and organization.

MR. MARKUS: Hi. Good afternoon. I'm Richard Markus. I've vice president of global development for Amgen's biosimilars portfolio. Although we are known for our innovative medicines, Amgen has 9 biosimilars in development, and we're using our 35 years of biologics manufacturing experience to develop our high quality candidates.

It's in this capacity that I'm here today, not to weigh in on the merits of this particular application, but as a biosimilar manufacturer, committed to the adoption of policies that will create a successful U.S. program whereby biosimilars are seen as therapeutic choices incorporated into the U.S. healthcare.

A successful biosimilar program is one where physicians and patients have confidence in biosimilar medicines, and such confidence is fostered by policies that ensure transparency of specific product information, accountability of the manufacturers, and traceability of what's been dispensed to the patients.

Policy decisions to achieve and maintain confidence must consider the landscape of 2015, but also 2020 and beyond. In 2020, for example, there could be 10 biologic medicines, each with 4 biosimilars. So including the referenced biologics, that's 50 unique products that need to be accurately tracked and traced, so that manufacturers can independently be accountable for the safety, purity, and potency of their products.

It's to those ends that we urge the FDA to adopt the following scientific and public health policies. One, non-proprietary naming should be distinguishable for every biologic, including biosimilars, to enable accurate medical records, manufacturer accountability, and informed appropriate use.

Two, product labeling should be specific and transparent. The prescribe information should identify the product as biosimilar or interchangeable, and should identify the pivotal clinical safety and efficacy data for the biosimilar. And three, when appropriate, postmarketing studies should be carried out to further assess immunogenicity in the most sensitive populations, especially if those are extrapolated indications.

Though they're not part of today's agenda, policies related to interchangeability designations must address both scientific and real-world considerations, including: requiring studies to address the most sensitive patient populations and multiple mechanisms of action; accounting for multiple interchangeable biologics, each compared only to the reference product and not to each other; and preventing inappropriate and inadvertent substitution of non-interchangeable biologics.

In summary, FDA should adopt policies that ensure data transparency, manufacturer accountability, and product traceability in order to facilitate a successful and sustainable biosimilar environment. Thank you.

DR. ARMSTRONG: Thank you. I'll invite speaker number 4 to come up. And again, please state your name and organization.

MS. CARDEN: Good afternoon and thank you to the FDA. My name is Mary Jo Carden, and I am here on behalf on the Academy of Managed Care Pharmacy, AMCP. I have no financial disclosures with the sponsor involved with this application.

Today, I am here to talk about AMCP's support of the development of a biosimilars pathway and not to weigh in specifically on this application. AMCP's 7,000 members nationwide provide clinical and business management services to more than 200 million Americans covered by a managed care pharmacy benefit.

AMCP's members' utmost concern is to provide access to high quality and affordable pharmaceuticals and biologics in the United States, and therefore, we support the development of biosimilars.

As we've heard today, biologics play an

increasingly important role in the U.S. healthcare system, particularly for the prevention, treatment, and cure of otherwise incurable or complex diseases. An approval process for biosimilars must support a balance between bringing safe and effective medications to market, while maintaining affordability.

The regulatory approval process must ensure rigorous examination of safety and efficacy of biosimilars, but not be overly burdensome to prohibit applications for approval.

AMCP supports the ability of FDA to set case-by-case basis on whether to require additional clinical trials prior to approval, and any postmarketing surveillance after approval. Postmarketing surveillance must be available to monitor safety and efficacy in large populations. This is a core component of AMCP's position.

Furthermore, to ease confusion among prescribers, pharmacists, and patients, approved biosimilars must be permitted to use the same international non-proprietary name as the referenced product. This will help encourage substitution of biosimilars, when appropriate, by ensuring consistency among products and ensure comparable safety and efficacy based on FDA standards.

The use of manufacturer name, national drug codes, or known as NDCs, and lot numbers may continue to be used to effectively differentiate batches for purposes of safety monitoring. FDA must provide specific rules for the designation of interchangeable products.

Thank you. I see my time is almost up. So with that, I will conclude by saying, thank you for the opportunity to present before the FDA today, and AMCP looks forward to continue working with FDA to ensure that consumers in the United States can receive access to biosimilar products. Thank you.

DR. ARMSTRONG: Thank you. Speaker number 5.

MR. KLIMEK: Good afternoon. First, I want to thank the committee for allowing me to speak today. My discussions will not be particular to

EP2006, but rather on biosimilars in general. My name is John Klimek. I'm a pharmacist. I work for the National Council for Prescription Drug Programs, NCPDP.

We are a not-for-profit organization that has about 1600 members that are pharmacy-based, and what we do is we develop standards that pharmacy uses today in all aspects of pharmacy. And you may also know us for our script standards that are being used between physicians and pharmacies in sending prescriptions back and forth.

I'm a pharmacist. I've dispensed medications for over 20 years. I've worked in a large managed care facility in Chicago. I was responsible for formula and benefit. I've done a lot of things with claims processing, so I'm very familiar with the process of dispensing and some of the pitfalls that pharmacists run into today, so, basically, I want to discuss some of that to you.

A little bit about NCPDP. We're a multi-stakeholder, problem solving forum. Again, we develop standards that are used in pharmacy. We also do best practices for patient safety, such as health literacy, safety use of acetaminophen. We also are advisor to policymakers. And again, our members, we have about 1600 members.

Within NCPDP, we have work groups and task groups. In particular, we have a task group that's dedicated towards naming standards for biologics drugs and biosimilars. Basically, this task group has looked at ensuring an accurate and consistent identification of drugs to meet the essential needs of the U.S. prescribers, dispensers, and claims administrators, again, preserving the fundamental goal of patient safety.

The role of the drug compendia that we have as part of our members actually is twofold. It's an integrative process where the raw data is provided. The end user must develop an interface application and can and will change data that is received, also used in pharmacy dispensing, as I mentioned earlier. And payer decision to reimburse, as well as content management systems use that information. They also provide reference information for drug reference, and there's a lot of activity going on there as well.

The compendia groupings are used as a basis for a variety of outcomes, again, for determining equivalent products and determining candidates for substitution. All will be disrupted if the naming conventions are changed. Each process will have to be individually rebuilt to ensure patient safety and restore functionality to the systems.

Applying different names for the same biological product is important, and it reduces confusion and unnecessary complexity. And again, it's one of the things that we're looking for, for the FDA to look forward to.

I'm sorry I went over. Again, thank you for my time with you, and I look forward to working with the FDA. Thank you.

DR. ARMSTRONG: Thank you. Speaker number 6.

MR. PHILLIPS: Good afternoon, my name is Thair Phillips. I'm the president of Retire Safe. I have no financial relationship with the manufacturer in today's hearing. Retire Safe is a nationwide non-profit advocacy organization for older Americans. I'm here today to represent our 400,000 supporters and to give a voice to those who will ultimately be patients receiving these new life-extending and life-enhancing medicines.

While the topic today is largely about one specific biosimilar application, the implications for patients extend beyond one drug. Our concern is for the safety of the patients.

To accurately represent our supporters, we reached out to them through a survey to measure what they know about biologics and biosimilars and the potential safety issues surrounding these new medicines. We asked a series of questions and then gave them a chance to comment. More than 1400 supporters responded to the survey, and the results were very interesting.

Survey response expressed overwhelming support for patient safeguards. Ninety-two percent of seniors want drug companies to test the safety of biosimilars for all conditions that they will be used to treat, and 80 percent want human clinical trials to take place. Ninety percent of seniors want each biosimilar product to have a different name than the original biologic so that patients and physicians can adequately track adverse reactions.

Ninety-four percent believe patients should be notified when a biosimilar is substituted for the original drug prescribed by a doctor, and 91 percent want physicians to be notified whenever such substitution happens.

We realize that asking questions that concern safety will usually bring a positive response, but there are two facets of this survey that deserve special attention. First, we have never had this magnitude of positive responses. I think this reflects the common sense thinking of our supporters, people who would say, why in the world wouldn't you test the medicine for all the conditions and do human trials like we have done for years? Why wouldn't you have a different name to reduce confusion and tell everyone if the medication is changed? It just made sense to them.

The second facet that was especially interesting is the written comments received. Again, the large number of people that responded is unprecedented. Here are two representative comments.

One person said, "No medication should be substituted without the permission of the patient. People should have information so they may make an informed decision regarding their health and medications."

Another person said, "I have had problems with a heterogeneric drug that did not have the expensive catalyst that helped the body absorb it correctly. It did not work at all. What can we expect of a biosimilar?"

As you can see, these people are concerned. Americans trust the FDA. As a voice for the people you protect, we ask that the FDA issue final guidance on these key issues and that Congress conducts appropriate oversight before the FDA gives final approval to the first biosimilar. To do otherwise will undermine patient confidence. Thank you.

DR. ARMSTRONG: Thank you. Speaker number 7.

MS. DORMAN: Good afternoon, and thank you for the opportunity to speak about a topic of significant importance to the National Organization for Rare Disorders. I am Diane Dorman, vice president of public policy at NORD. By way of disclosure, I'm appearing solely on NORD's behalf and have no financial stake in the outcome of anything I will be discussing. I am also a member of Patients for Biologic Safety and Access.

NORD represents 30 million patients with rare disorders and their families. Many of their patients receive biologics or have taken them over the course of a disease crisis. We applaud the industry for developing these groundbreaking innovative therapeutic treatments that have benefited so many patients. We also applaud FDA, which has done so much to foster a regulatory environment in which safe and effective biologics can be developed and add significant value to rare disease patients.

NORD welcomes the coming introduction of biosimilars in the marketplace. Biosimilars are highly similar, but not identical versions of the original product. They should be less expensive, and thus enhance patient access in situations where medical costs are a barrier. With the proper ground rules, biosimilars should be a boon for patients.

We also see biosimilars having an important role in biomedical innovation for the next decade. There is the obvious reason. As originator, products face increased competition from biosimilars, companies will be looking to develop a greater number of innovative products, as well as finding ways to improve their existing biologics.

Also, biosimilars should stimulate increased research into the characterization of biologic molecules. The resulting knowledge will be just as valuable to innovators as producers of biosimilars.

A minute ago, I referenced the ground rules under which biosimilars will be permitted to come to marketplace. It is here that NORD has concerns, and has sought multiple forms to express those concerns.

A chief concern is the naming of biologics, including biosimilars. For rare disease patients, distinguishable names for biologics are a fundamental core of maximizing the benefits and minimizing any potential harm from biosimilars. Without distinguishable names for biologics, there is a significant risk to our community that prescribers and payers will gloss over the critical difference between identical generic chemical compound drugs and highly similar biosimilar biologics.

Rare disease patients are often among those most sensitive to even small differences among products. To protect a rare disease patient, distinguishable names are needed to that every patient, prescriber, payer, and pharmacist can be certain that the products will be dispensed properly.

Again, thank you for the opportunity to speak today and share the views of the rare disease community. We look forward to the benefits that biosimilars promise to provide all patients and look forward to continue to work with the FDA to promote medical innovation. Thank you.

DR. ARMSTRONG: Thank you. Speaker number 8.

DR. NIAZI: Good afternoon. My name is Sarf Niazi. I'm the CEO of Therapeutic Proteins International, out of Chicago, and a competitor to both Sandoz and Amgen, and therefore, unfortunately, we have no conflict of interest with either company.

We have three points to make. First, while Sandoz suggested, and FDA agreed, that their product is highly similar, which is the minimum gateway to 351(k) filing, my question is, why did Sandoz not assert for fingerprint-like similarity -- a word that I've not heard all day long -- and if they had, would FDA agree to that?

We feel Sandoz has done a great job, and this product should qualify for a fingerprint-like similarity. We know what it takes to make one. But this also is significant because that reduces the burden of residual uncertainty removal, and also this will help establish the standards of what is highly similar and fingerprint like for the future.

Second, FDA has iterated that the safety and effectiveness of filgrastim are better studied in healthy subjects. My question is, would FDA reach the same conclusion about Sandoz's product if they did not have the study 302 or the clinical study? We think FDA should have. And this will also be an important statement to make for the record.

The third, we would like to know the scope of the label that the FDA would approve for Sandoz, and also the name designation they are ready to give to Sandoz.

With those comments, we strongly urge the committee to give its full approval. And I want to thank FDA for this remarkable high standards of transparency that we have observed today. Thank you.

DR. ARMSTRONG: Thank you. Speaker number 9.

MS. ARNTSEN: Good afternoon. My name is Kathleen Arntsen. I'm president of Lupus and Allied Diseases Association, but I'm here today as a patient. I have nothing to disclose. I realize the tremendous promise and therapeutic advantages that biosimilars hold for patients like me, just as biologics like Neupogen have for millions living with life-threatening and life-diminishing diseases.

Lupus is an extremely complex, chronic inflammatory, autoimmune disease affecting virtually any organ of the body. With no known cause or cure and few treatments, it is highly individualized, extremely volatile, debilitating, life-altering, and potentially fatal.

Like others with lupus, I suffer from several autoimmune disorders and comorbid conditions, including neutropenia. I take 35 medications per day and have unique allergies and sensitivities to both active and inactive ingredients in drugs.

As you review the first biosimilar application, I ask you to please establish a policy for biosimilars regarding safety, efficacy, informed choice, distinguishable naming, and postmarketing surveillance.

You must remain vigilant in protecting patient safety, while promoting unfettered access to vital and effective treatments by recognizing the complexity of biologics snowballing with each generation, as well as the intricacy and vulnerability of the potential patient populations.

It is essential that biosimilars are approved as being highly similar to the original product, and sufficient proof of clinical efficacy, safety and tolerability is provided.

Please understand no one size fits all products exist for complex patients like me. Our response to treatments is unique, contrary, and at times adverse. Pharmacovigilance is essential because biologics produce idiosyncratic and immunogenic reactions in patients who can also be hypersensitive to changes in production methods or impurities. Adverse effects are difficult to predict, and may only occur after many years of treatment.

I ask you to require the establishment of distinguishable, non-proprietary names for the proposed biosimilar. This will avoid confusion with Neupogen and ensure accurate physician/patient communication, as well as reliability of the prescribing, dispensing, and compliance processes of the specific therapy. A

Applying unique non-proprietary names will create clarity, facilitate prompt accurate association between adverse events and specific products, thereby maintaining drug manufacturer accountability for their product and enabling the healthcare community to better address any potential adverse events.

Due to the heterogeneous nature of autoimmune diseases like lupus, no two cases are alike and treatment is highly individualized. Only healthcare professionals familiar with my personal medical history, including known sensitivities and past complications, should be making my treatment decisions to balance therapeutic and safety concerns.

It is imperative that we have the necessary material to make completely informed decisions regarding the choice to use a biologic or biosimilar, and I also feel that automatic substitution of biosimilars for biologics disrupts continuity of care, and is absolutely unacceptable. I thank you for the opportunity to share my perspective.

DR. ARMSTRONG: Thank you. Speaker 10.

DR. ROACH: Hi. My name is Jim Roach. I'm the chief medical officer of Momenta Pharmaceuticals. Momenta and Sandoz are partners on the development of two complex generics, enoxaparin, Lovenox, and Copaxone, glatiramer acetate, but we have no relationship in biosimilars.

Thank you for the opportunity to speak today on the importance of both interchangeability and extrapolation of indications in order to realize the full potential of the 351(k) pathway.

Momenta's applied the concepts of thorough structural and functional characterization to the development of complex generics, biosimilars in autoimmune and oncology, and novel drugs. We believe our experience in developing enoxaparin has provided some unique insights into biosimilar development.

Enoxaparin is relatively an expensive drug, and yet we estimate that the healthcare system has saved over $2 billion since launch. As enoxaparin was approved under the ANDA pathway, extrapolation and interchangeability were assumed, but clearly interchangeability was the major driver for the cost savings.

Two articles authored by FDA and published in leading scientific journals noted that the scientific principles applied to the review of a generic enoxaparin are also relevant to biosimilars, and that extensive analytical characterization may help to reduce the scope and extent of clinical studies for biosimilars. For enoxaparin as an aside, no clinical safety and efficacy trials were required for approval.

Many stakeholders argue that biologics are orders of magnitude more complex than small molecules and are impossible to fully characterize. Further, the process is the product and cannot never be truly understood or replicated. This logic is then used to conclude that multiple large equivalence trials should be required in each and every indication to confirm safety, efficacy, and comparable immunogenicity.

I note this figure from and American Cancer Society Cancer Action Network commissioned primer entitled, Understanding Biologic Medicines from the Patient's Perspective. Soups, or complex mixtures like enoxaparin, were depicted here as being equally or perhaps even more complex than monoclonal antibodies.

Biologics are most certainly complex, but the science of analytical comparison has evolved considerably since the first biologics were approved. These challenges are tractable, and interchangeability of complex drugs is most certainly achievable.

Many different stakeholders advocate for various policies with the preface, patient safety is the paramount concern, but there's also often an associated inference that somehow biosimilars will be unsafe and put patients at risk.

The patient holistically, inclusive of cost and access considerations, should be of primary concern, and equal emphasis should be placed on the benefits of biosimilars. They'll be highly scrutinized and undergo a very intensive review. And for biosimilars that meet the high standard for approval, comparable safety and efficacy can and should be assumed by patients and physicians, a message which is being actively disseminated I know by EMA regulators.

This speaks to the point that education of clinicians and patient groups on the biosimilar paradigm will also be critically important to the success of the pathway, and rhetoric and misinformation from certain stakeholders needs to be replaced with unbiased objective and scientifically based information.

So in summary, granting of indications and designation of interchangeability, when appropriately scientifically justified, will maximize success and utilization of the 351(k) pathway and lead to the greatest cost savings. Thank you.

DR. ARMSTRONG: Thank you. Speaker number 11.

MR. MARMARAS: Good afternoon. My name is Stephen Marmaras. I'm the manager for state and national advocacy with the Global Healthy Living Foundation. I have no disclosures to make regarding my travel here today.

The Global Healthy Living Foundation accepts grants and charitable contributions from pharmaceutical companies, government, private foundations, and individuals. We have received scientific briefings from pharmaceutical companies as well as from our independent medical advisory board.

GHLF is a 501(c)(3) patient group that works to improve the quality of life for people with chronic disease, often focusing on those least able to advocate for themselves. We work to expand access to new and improved medical treatments, such as biologics and biosimilars, for patients. We share the same goal as the FDA and this committee in ensuring the biologic and biosimilar safety should be of paramount concern.

Biosimilars represent great potential for patients. When these products are eventually approved in the U.S., they will expand access by offering new treatment options for patients like Kimberly in Delaware, who has exhausted trying nearly every current biologic on the market.

Biosimilars also offer the potential of much needed cost savings, with estimates of between 10 and 30 percent. For single moms with mounting medical bills, like Stacy in Idaho, biosimilars can lift a financial weight from their shoulders. In short, biosimilars represent hope for patients, hope for healing, and hope for a better future.

But will patients have any hesitancy to adopt these new products? The patients in our community say yes. In fact, we asked them specifically what they would like to see from biosimilars before they felt comfortable taking them.

These are the three attributes that they deemed critical. Number 1, support services. Do support services that accompany a biosimilar therapy measure up to the best services individuals have received in the past?

Number 2, data transparency. Is there clinical trial data that show this drug has been tested and proven to be therapeutically similar? Patients want to know how similar a biosimilar really is. Or in other words, they want a variance index against innovator drugs.

Lastly, naming. Biologics and biosimilars should have distinguishable naming system. Our patient advocates urge the FDA to finalize a guidance that calls for the use of distinguishable names for biologics and biosimilars.

Millions of U.S. citizens with chronic disease, as well as cancer and bone marrow transplant, who would specifically use the Neupogen biosimilar, are desperately awaiting the arrival of biosimilars and the incredible value they could offer. If issues impacting patient confidence are not addressed, this value will never be realized.

As the FDA continues to evaluate biosimilars for approval in this country, we urge the agency to address these areas they have control over that patients in our community have clearly identified. We welcome input and collaboration. Thank you for your time an attention.

DR. ARMSTRONG: Thank you. Speaker number 12.

MR. SPIEGEL: Good afternoon. I have no financial relationships to disclose. My name is Andrew Spiegel, and I'm the executive director of the Global Colon Cancer Association, a patient organization, which is the voice for 6 million colon cancer patients worldwide.

The GCCA unites patients from all corners of the world in the fight against colon cancer and is increasing access, earlier diagnosis, and awareness, so that people have access to treatment for a disease that kills more than 600,000 people worldwide.

Before running the GCCA, I was the CEO of the U.S.-based Colon Cancer Alliance, the oldest and largest national patient advocacy organization, advocating for the 1.2 million colon cancer patients in the U.S.

I personally know the impact of cancer, having lost both of my parents, two days apart, from the disease, 15 years ago next week. I lost my mom to colon cancer two days after losing my dad to pancreatic cancer. In fact, I can recall my mother taking this exact drug that's up for review here, and I remember her giving it a pet name, Neupy [ph]. And she would know when she needed to go to the hospital to get Neupy to feel better, and I personally witnessed her feeling much better after receiving this drug.

We wish preventive methods alone were sufficient to defeat colon cancer, but we know that the reality in this country is far different. Over the past 15 years in the advocacy world, I have personally seen the impact biologic medicines have had in the colorectal cancer community.

When we look at progress over the last 15 years, we see that the average metastatic patient is now living three times longer than before the introduction of biologic medications. We're looking at an average of 9 or 10 months to now knocking on the door of 3 years.

We look forward to biosimilar medications being introduced to the U.S. market. We know that lower cost medications mean more access, more lives saved, and better quality of lives for patients. Yet we recognize the inherent safety challenges associated with this class of medications for policyholders such as yourselves.

On behalf of the patient community, I applaud the FDA for its longstanding commitment to patient safety and feel there are certain elements a biosimilar policy should have to achieve our common goal of enhancing access to life changing therapies.

Fundamentally, patients want to know that we can expect the same safety, purity, quality, and efficacy from an FDA-approved biologic that we can from an FDA-approved reference biologic. The level of confidence can only come from data, which demonstrates therapeutic equivalence over large populations.

We also feel that another key to effective pharmacovigilance would be for the FDA to require non-proprietary names distinguishable from the reference biologic. Biologics, we know, are extending the lives, reducing the suffering caused by disease, and giving optimism to millions of patients. And while we all want to reduce the cost of medicines, we don't want to do that if the drugs aren't safe. Thank you for considering our perspective.

DR. ARMSTRONG: Thank you. Speaker

number 13.

MS. LEONG: Good afternoon. My name is Amye Leong. I'm delighted to be here. I am spokesperson and director of strategic relations for the United Nations endorsed Bone and Joint Decade, which operates in 63 countries, including the United States. I'm also chair of the California Arthritis Foundation. But most importantly I'm here because I'm a patient. I'm a patient with a life-threatening disease, who has experienced many of the things that were cited this morning.

I'm here of my own accord, my own expense, because I do believe that the FDA, God bless you, is at a critical juncture. And with the sponsor's application, I think that this really opens up an opportunity, not only for people who have spoken before me, but for the future path that you are carving, and more patients like me, my people, need to be heard from about this particular issue.

I'm a patient with a serious life-threatening disorder that so far, to date, has put me in the hospital -- and almost died four times -- for 293 days. I have had blood disorders. I have went experienced different pheresis. As a result of that particular disease, I've had to undergo 28 surgeries, 16 of those were joint replacements.

I'm standing before you today in little tiny heels as a testament of not only the medicine that's available, but the gumption that patients and patient advocates and their families have to have.

We have talked this morning about the elephant in the room, about cost. And I know that the FDA is not to be talking about this, but it is the cost that we patients daily must deal with. It is the cost, the loss of money, about healing from, or trying to get better and get well and get through this disease for which there is no cure.

It is the cost to our families and to our children, and to the household, because when we cannot move, and do, and work, and play, the cost to a quality of life. So that cost, we look to you to help set that standard and you as the FDA. And the fact that you are looking at his case-by-case is extremely important. We trust you. We patients trust you. I trust you.

I trust you enough that I had to come here and let you know that it's important enough for me, as you set this first critical pathway to move forward, that it makes sense, and that the issues that have previously been addressed by previous speakers will come and be looked at by you in due time, but we hope that you will encourage us to participate.

The other piece is about access. There are people of color, like me, I come from an Asian background, who have zero choice because of their lack of health literacy, their lack of access. And it's biosimilars that can really play an important role. So we thank you and hope that you will vote in favor of this application. Thank you.

DR. ARMSTRONG: Thank you. I'll invite speaker number 14 up now.

MR. HOUTS: Good afternoon. Jonah Houts,

Express Scripts. I have no financial relationships to disclose. Thank you for the opportunity to be here today. Express Scripts is the nation's largest pharmacy benefit manager. So on behalf of 90 million different Americans, be it through their insurers, their employers, a Taft-Hartley Union Fund, Medicare Part D, state and local government, we're helping manage the prescription drug benefit to make sure cost effective, clinically appropriate benefits are available.

Now, in 2014, we adjudicated 1.4 billion prescription drug claims here in the United States. And I can tell you with that type of experience, unique international non-proprietary names are not necessary. When you combine FDA and state regulation of prescription drug labels, as well as the aforementioned MCPDP data transaction systems, information about what actually was dispensed at a pharmacy is available to physicians through medication history. So the application of really 21st century technology helps obviate that concern.

But Express Scripts is also the nation's largest specialty pharmacy, serving patients across the country who use these costly and complex therapies. For years, we've been talking to our clients and patients about the opportunity that a robust, biosimilar marketplace would bring.

These large insurers, these Taft-Hartley Plans, these small employers who are just trying to manage a budget for a dozen employees and their beneficiaries, they need your help. They need your help in two ways.

First, they need lower cost treatments. And I know it's already been said, but Express Scripts examined U.S. sales for the product in question here and believe there's a $5.7 billion savings opportunity in the United States over the next 10 years. Second, these clients need expanded access to new treatments, and they want to expand access to new treatments.

Here's what I mean. Even when patients have coverage, lower treatment costs expand access to more therapies, at earlier intervals, in the treatment of disease. And we also believe that there is an opportunity for additional research and development in the biotech space once competition takes hold. Our country's recent experience with costly, complex antiviral drugs makes this case very clear. When more competitors produce therapies, costs are lowered and access is expanded.

As the nation's largest specialty pharmacy, the most clear mandate we have for biosimilars comes from our patients; these patients who are making daily tradeoffs in their own homes and in their budgets. These are our neighbors. They are our friends. They are our children. They are our parents. And they need your help.

So Express Scripts implores the committee to report favorably on this filgrastim biosimilar application to lower medication costs and expand access to affordable medicines for all Americans. Thank you.

DR. ARMSTRONG: Thank you. Speaker number 15.

DR. YAPUNDICH: Good afternoon. Thank you for the opportunity to join you today as you consider filgrastim and future biosimilars. My name is Robert Yapundich. I'm a practicing neurologist in the big city of Hickory, North Carolina.

I am speaking today on behalf of the Alliance for Patient Access, a national organization of over 400 physicians advocating for patient access to approved therapies. As a neurologist caring for people with multiple sclerosis, cervical dystonia, migraine, and even post-stroke spasticity, it is such an honor to be a physician when so many groundbreaking therapies become available for diseases, where previously I had very limited treatment options.

As the FDA evaluates filgrastim, may I ask that you take this unique opportunity to forge a solid precedent for future biosimilars, and make patient safety your top priority by considering the importance of distinct, non-proprietary names, as well as a distinct biosimilar approval process for each indication.

Distinct names for all biosimilars and biologics allows for immediate and clear delineation for these medications, and would represent an important step forward to a more worldwide, uniform standard that endorses the position advocated by the World Health Organization.

Ultimately, distinct names will allow patients and healthcare providers to clearly distinguish medications within a class and improve therapeutic vigilance and post-approval surveillance as it pertains to our ability to prescribe, monitor, and accurately assess our patients' response to these therapies. A transparent and unique naming system is essential and effectively creates another layer of patient protection.

The second priority pertains to the comprehensive clinical trials for each biosimilar approved indication. As a neurologist, I have come to appreciate the complex, tremendously beneficial, yet unpredictable nature of biologics that I use to treat my patients with neurodegenerative disorders in my practice, such a multiple sclerosis. These are incredibly disabling disorders where a lack of efficacy translates into permanent loss of brain tissue and function.

By pursuing a policy of indication, extrapolation, the FDA would be focused on improved access and costs, while compromising drug efficacy and patient safety. These complex molecules cannot, and should not, be regulated in such a simplistic manner.

In summary, I urge the FDA to act in a manner that places patient safety first and promotes pharmacovigilance by adhering to a policy requiring distinct names and comprehensive clinical trials for each approved indication.

I urge you to create a solid foundation of approval policy for biosimilars that starts with filgrastim and continues with future biosimilars. Anything short of these requirements is a strike against patient safety and biosimilar medication access. Thank you.

DR. ARMSTRONG: Thank you. Speaker number 16.

MR. LAMOTTE: Hi, my name is Larry LaMotte, and I'm vice president of public policy with the Immune Deficiency Foundation. And the Immune Deficiency Foundation is the national nonprofit organization who represents patients who are born with a malfunctioning or nonexistent immune system.

We believe that patients really need be a part of this discussion, and be a part of the drug making process within the FDA process itself. We think that our -- as part of that, IDF has been one of the organizers of a patient coalition, called Patients for Biologics Safety and Access, and we have communicated with the FDA on a number of issues. I'm here today on behalf of IDF, though.

Primary immunodeficiencies, as I said, represent diseases with a malfunctioning or nonexistent immune system. Most of our patients cannot produce antibodies, and therefore need a product called an immunoglobulin, or blood plasma product, in order to have a relatively healthy normal life, which is infused intravenously, maybe once a month, for the rest of their life. This is not a short-term, but a long-term use of a biologic immunoglobulin. It is expensive. A single treatment can cost thousands of dollars.

We believe that biosimilars provides a very good hope for access to treatments, and we hope that the FDA will have a framework that is open and transparent as we go through the process. I know that it is interested in a case-by-case basis for everything, and that's fine, but there needs to be a better roadmap and rules of the road that are clearly identifiable for transparency purposes in the drug development.

We are concerned about a few key topics. First, we believe that biosimilars should have distinguishable, non-proprietary names. We are concerned that a shared, non-proprietary name implies interchangeability, even in cases where the agency has not made such a filing. In addition, a distinct name will facilitate faster tracking of products in the event of adverse events.

Secondly, while the FDA views its role as strictly limited to an assessment of similarity to the reference product, we urge the agency to also assess the safety and efficacy of the biosimilar in its own right. We also urge the agency to require specific data for each indication for which the manufacturer seeks to market a biosimilar product.

Finally, while it's not the concern of the FDA, we are very concerned about the switching of stable patients to new products. We know the experience from our patient experience is that if they're switched to a new product, up to 30 percent will have an adverse reaction. That's not me talking, that's peer-reviewed literature. We thank you very much for this opportunity to speak to you, and I thank you for your time.

DR. ARMSTRONG: Thank you. Speaker number 17.

DR. RAMACHANDRA: Good afternoon, and thank you for the opportunity to address the committee. My name is Sumant Ramachandra, and I speak to you today both as a physician and the chief scientific officer of Hospira, the world's leading provider of injectable drugs and infusion technologies. And obviously I'm already at conflict because we do compete directly at this point in Europe with Sandoz as well as Amgen, the originator, in both the biosimilar space and generic space.

The decisions before you will become a history making event in the United States for many stakeholders, but most importantly the patients and families who will have greater access to lower cost and safe and effective medicines that can improve health and save lives.

Hospira is the only U.S. company marketing biosimilars for over 7 years in the highly regulated markets of Europe, Australia, and more recently, Canada. Hospira's three biosimilars to date are filgrastim, which you're hearing today, epoetin, and infliximab, and we have others planned in our pipeline.

Across these three products and millions of patient doses administered, we have seen a safety profile similar to the reference products, and a significant reduction in cost to patients and healthcare systems. Most importantly, biosimilars have opened up greater access to patients for biologic medicines.

We are pleased that this day has finally arrived in the U.S. It is important to remember that, without competition, reference biologics can be very expensive drugs, costing as much $100,000 a year or even more. Biosimilars are expected to bring savings and provide better accessibility to patients, and our experience in Europe does support this.

Biosimilar product development is rigorous and challenging. Each program is unique, robust, and scientifically tailored, and follows careful stepwise approach to development. As you saw today, the foundation for biosimilar approval is a comprehensive, comparative, bioanalytical characterization program that are supported by comparative nonclinical and clinical data.

Approval of a biosimilar should be based on high similarity to the reference product. Modern analytical tools have the ability to discern differences that would not be detected in clinical studies. Indeed, clinical studies on biosimilars are conducted to confirm the high similarity established by the analytics rather than to reestablish safety and efficacy.

Another important concept is extrapolation. Extrapolation is the most important and fundamental underlying tenet for the sustainability of the biosimilar pathway. Extrapolation must be granted when scientifically justified. Extrapolation is based on the comparison of the totality of evidence comparing the biosimilar to the reference product. And it's been allowed in Europe, as well as in other markets to date, based on the scientific justification.

We commend the FDA for following an open public process. The biosimilar pathway is novel, and the stakeholder input is important, and education process is critical for successful regulatory approval and adoption of biosimilars. We look forward to a day when patients and healthcare providers can utilize biosimilars, and we appreciate the opportunity to speak to this panel. Thank you.

DR. ARMSTRONG: Thank you. And speaker number 18.

MS. CRYER: Good afternoon. My name is Donna Cryer, and thank you for this opportunity to comment on these proceedings. I have no conflicts of interest.

Although I am incredibly honored to serve in many advisory capacities for several federal and nonprofit entities, including NIH, the American Board of Internal Medicine, the Personalized Medicine Coalition, and the Global Liver Institute, today I speak only as a person whose life depends on biologics.

As a patient living with multiple manifestations of autoimmune diseases over more than 30 years, including inflammatory bowel disease, rheumatoid arthritis, and being actively monitored for several pre-cancerous conditions, I have exhausted the effectiveness of many medications, and now rely primarily on biologics to be able to eat, eliminate, walk, work, or live my life.

Biosimilars may increase access to potent and important medications to a larger number of patients. However, I ask you to keep foremost in your mind that my doctors and I carefully balance the administration of my biologic therapies with my individual immune system to avoid infections, development of blood cancers, and many other dangerous side effects, and we do this with relatively limited monitoring technology.

We need to be absolutely clear about the medications that I am taking, and I have the right to make truly informed choices about these medications. Allowing branded biologics and the biosimilar to have the same name violates both of these principles.

Biosimilars are not biosames, and my doctors don't pour out active ingredients into my hands, they inject specific products into my veins. We have enough variables in managing biologics interacting with other prescriptions and conditions, and my immune system, without interjecting the uncertainty and the burden of having to investigate the source of medication at every administration to ensure consistency of care and response.

I ask that if this, or any biosimilar product is approved, that it be given a distinguishable name, identifier or modifier, which I understand would align with both the USAN Council and World Health Organization providing global consistency.

This would not create confusion for patients and doctors, but on the contrary, would provide clarity and confidence in the biologics we would be using, ensure greater stability and safety in clinical practice, and allow for greater precision in postmarket surveillance and research in both safety and efficacy. Thank you.

DR. ARMSTRONG: Thank you very much.

The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience.

Following the break, the committee will turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments. I would remind the panel members we're not to discuss the issue at hand amongst ourselves. We'll now take a 15-minute break and return at 3:35. Thank you very much.

(Whereupon, a recess was taken.)

Questions to the Committee and Discussion

DR. ARMSTRONG: Thank you very much. If you could take your seats. We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

FDA will now read the questions to the committee.

DR. DEISSEROTH: Question number 1. This

question is for discussion. Does the committee agree that EP2006 is highly similar to the reference product, U.S.-licensed Neupogen, notwithstanding minor differences in clinically inactive components?

DR. ARMSTRONG: Thank you. And we have two questions. I think we'll address them one-by-one. Yes, okay. So could we go back to question 1? We'll address that one. So discussion from the panel?

DR. HILLARD: Yes.

DR. ARMSTRONG: I will say, I think we have the opportunity here -- obviously, this is the first of these biosimilars, but we have a product that in some ways there's very extensive data with regard to some of the required components, but also looking at a company that's -- this has been utilized extensively in other areas of the world. So I think there's fairly robust safety and efficacy, outside the United States, and that certainly makes some of this a little bit easier.

Obviously, the more detailed analytic

analysis and preclinical and clinical data than we're used to seeing here at ODAC. Did I see a hand over here?

DR. FOJO: And just by the way, the same thing. So obviously it's identical in terms of amino acid composition, so even more than highly similar. It's formulated differently, and that leads, we believe, some of us here, to different properties. But then clinically, it is highly similar. Clinically, again, because it had a high starting point and 80 percent of a lot is still a lot. So the answer is --

DR. ARMSTRONG: And do you agree that those differences are minor?

DR. FOJO: I think, as far as clinical activity, they end up being minor.

DR. ARMSTRONG: Dr. Waldman, do you agree?

DR. WALDMAN: Yes, I'm going to go with my colleague on this. I remain a little skeptical.

DR. ARMSTRONG: Any other discussion?

(No response.)

DR. ARMSTRONG: I guess we can move to

question 2.

DR. DEISSEROTH: Question number 2 for discussion. Does the committee agree that there are no clinically meaningful differences between EP2006 and U.S.-licensed Neupogen?

DR. ARMSTRONG: Any discussion? Maybe this is where you want to bring up your concerns and issues. I mean this is --

DR. WALDMAN: It's just for discussion. It's not a concern.

DR. ARMSTRONG: That's exactly what this is.

DR. WALDMAN: It's just for discussion. So a number of us were talking about the differences that we found before, and there are two pieces to the issue. One piece of it is, the numbers are different in the two data sets that we looked at, and we're still scratching our heads why those numbers are different.

Don't know the source of the differences, but clearly, if they were the Sandoz numbers, everybody would be happy and there wouldn't be this question. If they're the FDA numbers, it sets a different tone for the discussion.

The second issue is, keying in on no clinically meaningful differences, it's hard to know if having three times the number of patients not come back, not hit the baseline for absolute neutrophil counts in one bucket versus the other bucket, is clinically meaningful.

The thing that mitigates that piece of the discussion is that it's been given 7.5 million days of dosing, and there are no differences that are at least obvious. But it still is of concern that there are three times the number of patients who didn't recover their neutrophil counts in one bucket versus the other, in one data set. That's the issue.

DR. ARMSTRONG: Dr. Neville?

DR. NEVILLE: I think Dr. Waldman summarized my concerns perfectly, and I agree with him.

DR. DEISSEROTH: May I respond?

DR. ARMSTRONG: Yes, please.

DR. DEISSEROTH: So the way you termed your concern was that there was a difference between the

Sandoz product and Neupogen in terms of the rate of recovery. And it's clear that the recovery curves to 5,000 from the nadir are identical, and even to 10,000. It's after recovery that you see these curves diverge at an absolute level that is far above the danger zone of severe neutropenia 500 and neutropenia a thousand.

So the recovery looks identical. Whether there is a real difference between those two molecules, we don't know. We've looked at those curves over and over again, and you there are many confounding factors in that trial that really prevent us from making a clear conclusion. But the recovery seems to be identical from a nadir.

DR. ARMSTRONG: Dr. Pazdur?

DR. PAZDUR: I think this is the reason why we have no clinically meaningful difference. It's not that there can't be any differences here, but is any difference clinically meaningful. And as Al mentioned, it's really that point when they hit the magic number, is what's the important issue, not what occurs afterwards.

DR. ARMSTRONG: Dr. Stroncek? Oh, sorry.

DR. BENSINGER: Yes. I think you're correct in terms of the curves. That reflects the median or the mean; I can't remember which one it was. We're talking about outliers, and there are significant numbers of outliers that don't reach a thousand neutrophils because they're still on treatment beyond this day 11. So that's, I think, what we were looking at.

Having said that, I'm convinced by the arguments of Dr. Cole and Mager that these are probably just the tyranny of small numbers, and that I think with a larger data set, you probably wouldn't see this difference.

DR. ARMSTRONG: From a clinical perspective, when you use these agents, first of all, number one is you're not checking blood counts every day. So the more common problem is that we overshoot, and that we then actually will take -- and the dosing is such that you don't really get to individualized dosing. You choose the 300 or the 480. And if you have somebody on the 480, and their day of treatment, their white count is 16,000, you say, well, maybe we should give them the 300 next time.

So there's a lot of empiricism to this, and all you need is a few patients whose body surface area or weight or whatever is off enough that they aren't really getting ideal dosing, and I think it is that issue of small numbers.

So I would say -- I'm not saying that there's no differences between these two, but I think clinically, these appear to really function pretty equally in terms of what you're asking them to do.

DR. NEVILLE: If I could just comment. I think at the end of the day, I agree with what's been said. No one can argue with the curves, but it would be helpful to have a clarification of which is the accurate data set because, one, then there's no question. And I would also argue that in pediatrics we do personalized dose, so differences do matter.

Vials? Yes, we actually do per kilo dosing. And so, it's a concern or a minor issue. I agree with my colleagues, but the two data sets are different. And it might have implications for pediatrics where we do personalized dose.

DR. KOZLOWSKI: Steve Kozlowski, FDA. So I think one of the things we heard at the beginning today was that this is a different paradigm, and this concept of totality of the evidence. So although it's very, very important to understand the details of every trial and what they mean, this is really confirming the highly similar, which everybody here I think was fairly quick to agree to.

So there's a tremendous amount of information that comes into this, speaking to similarity, from all the analytics. So even though it's very important to analyze the trials, and this is the correct thing to do, to think about them alone, again, as this is an independent study of safety and efficacy, isn't really the question.

The question is, does this confirm the idea that these are no clinically meaningful differences in the context of all the other data that has been built up in a stepwise fashion.

DR. ARMSTRONG: Any other comments? Yes?

DR. STRONCEK: Concerning the five indications, one of them is mobilizing hematopoietic stem cells, and that would include healthy subjects, be it HLA-compatible sibling donors, unrelated donors.

I think one of the clinical issues is adverse effects. And I think with the data we've seen today, we know that there's no difference in the common and expected adverse effects between EP2006 and Neupogen, but we don't know anything about the data presented about rare or long-term events.

Now, the fact they've given this for years in Europe makes us feel pretty comfortable that that's the case. I don't think it's a huge concern, but just based -- if it wasn't for that, I think I'd have a hard time voting for the question as far as safety for that particular indication.

DR. ARMSTRONG: Any other comments?

DR. LAPORT: Ginna Laport. I'd just like to say that I agree. I think the whole room agrees that we just need to reconcile the data sets. I don't know if it was transcription error, but we need to reconcile the data sets. But I also agree with Dr. Deisseroth and people on that side of the room that we all -- at the end of the day as clinicians, we care that our patients recover their neutrophils in a clinically meaningful, rapid way, and there's no question that both groups did that.

I agree that once a neutrophil count goes above a thousand -- especially me as a bone marrow transplant doctor, anything above 500 is great. But in reality, we want over a thousand, and 5,000 is amazing. So I think, again, it is definitely clinically meaningful that they're above a thousand. And I don't think it's enough -- not enough clinical meaningful in a negative way that they weren't all 5,000 at best, both groups weren't equal. So I think we're all kind of saying the same thing, and I think I'd answer yes to question number 2.

DR. ARMSTRONG: So I guess if I could

summarize, we have a lot of analytical data that these are very similar compounds. The pharmacokinetics and the pharmacodynamics are very comparable. There are some data set issues that we would have liked to have seen rectified, but that at the end of the day, the panel agrees that these are fairly similar compounds in terms of what we're asking these drugs to do.

I think we can actually move on to the vote, if there's no further discussion. We'll use an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote, or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. Barring questions, we'll proceed to the vote process.

DR. DEISSEROTH: So the question for voting, does the committee agree that based on a totality of the evidence, EP2006 should receive licensure as a biosimilar product for each of the five indications for which U.S.-licensed Neupogen is currently licensed?

DR. ARMSTRONG: So barring any questions, please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote, or you wish to change it, please press the corresponding button again before the vote is closed.

(Vote taken.)

MR. BRIGGS: The vote is 14 yes, zero no, zero abstentions.

DR. ARMSTRONG: So we'll go around the room. Dr. Fingert, you're nonvoting, correct? You're nonvoting, correct? Okay. So please give your name and your vote into the record.

DR. MOREIRA: Antonio Moreira. I voted yes.

DR. STRONCEK: I'm Dave Stroncek. I voted yes.

DR. MAGER: Donald Mager. I voted yes.

DR. WALDMAN: Scott Waldman. I voted yes.

DR. NEVILLE: Kathleen Neville. Voted yes.

DR. BENSINGER: William Bensinger. Yes.

DR. LAPORT: Ginna Laport. Yes.

DR. FOJO: Tito Fojo. I voted yes.

DR. ROTH: Bruce Roth. Yes.

DR. ARMSTRONG: Deb Armstrong. Yes.

DR. COLE: Bernard Cole. I voted yes. What really moved me was the very strong evidence shown by the sponsor for biosimilarity evidence: numerous studies, the structure, function, clinical performance of EP2006.

Although there appears to be some

possibility of small differences in some PK parameters, the clinical results demonstrate equivalence in a critically important endpoint, namely duration of severe neutropenia, with the best evidence along these lines being from the 302 study, which showed a mean difference in DSN between a negative .21 days to a positive .28 days, based on a 90 percent confidence interval.

This result is quite convincing when combined with the other data presented, although I will note that had that confidence interval been bumping up against the plus one or negative 1 days of difference, it might have been a harder decision.

DR. LIEBMANN: Jim Liebmann, and I voted yes for all the reasons that Dr. Cole stated. And since I have the microphone, I'll add the editorial comment, I was impressed that so many of the public statements had to do with the name of the drug. I think that this has been pretty clearly shown to be filgrastim, in fact, and I think that to name it anything else would be misleading.

DR. ZONES: I'm Jane Zones, and I voted yes. And I'd like to -- it's one of the easier decisions I've made on this committee. And I'd like to commend the sponsor and FDA for the quality of their materials and presentations.

DR. HILLARD: Hi. I'm Randy Hillard. I'm your patient representative. I voted yes, and I'm willing to bet my life on it.

Adjournment

DR. ARMSTRONG: That's a good way to end the discussion.

So now that the vote's complete, we will adjourn the meeting. Panel members, please remember to drop off your name badge at the registration table on your way out so that they can be recycled. Thank you everyone for all your hard work today.

(Whereupon, at 3:54 p.m., the meeting was adjourned.)